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HEALTH-RELATED QUALITY OF LIFE, SYMPTOMS AND COMORBIDITY IN INFLAMMATORY BOWEL DISEASE

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ACADEMIC DISSERTATION

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List of original publications

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III Haapamäki J, Roine RP, Sintonen H, Turunen U, Färkkilä MA, Arkkila PET. Health-related quality of life in inflammatory bowel disease measured with the generic 15D instrument. Quality of Life Research 2010;19:919-928.

IV Haapamäki J, Roine RP, Turunen U, Färkkilä MA, Arkkila PET. Increased risk for coronary heart disease, asthma, and connective tissue diseases in inflammatory bowel disease. Journal of Crohn's and Colitis 2011;5:41-47.

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Abbreviations

5-ASA	5-aminosalicylate
15D	15-dimensional
ANOVA	analysis of variance
CARD	caspase-activating recruitment domain
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDEIS	Crohn's disease endoscopic index of severity
CHD	coronary heart disease
CI	confidence interval
CIA	confidence interval analysis
CRC	colorectal cancer
CRP	C-reactive protein
CT	computed tomography
DBE	double-balloon enteroscopy
EFCCA	European Federation of Crohn's and Colitis Associations
ESR	erythrocyte sedimentation rate
HRQoL	health-related quality of life
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
IBS	irritable bowel syndrome
IC	indeterminate/unspecified colitis
IL	interleukin
IPAA	ileal pouch-anal anastomosis
IRR	incidence rate ratio
MRI	magnetic resonance imaging
NHP	Nottingham health profile
NOD	nucleotide oligomerisation domain
NSAID	non-steroidal anti-inflammatory drug
OEGD	oesophagogastroduodenoscopy
OR	odds ratio
PDAI	perianal Crohn's disease activity index
PGWB	psychological general well-being
PSC	primary sclerosing cholangitis
QALY	quality adjusted life year
RFIPC	rating form of inflammatory bowel disease patient concerns
SBE	small bowel barium examination
SD	standard deviation
SES-CD	simple endoscopic score for Crohn's disease
SF-36	medical outcomes study short form
SIBDQ	short-form inflammatory bowel disease questionnaire
SIP	sickness impact profile
TLR	toll-like receptor

TNF	tumour necrosis factor
UC	ulcerative colitis
VAS	visual analogue scale
WCE	wireless capsule endoscopy
WHO	World Health Organization

Abstract

Background: During the last decades, health-related quality of life (HRQoL) measurement has become an important outcome in treatment studies and in health policy decisions. Inflammatory bowel diseases (IBDs) are chronic gastrointestinal diseases of unknown aetiology. Symptoms of IBD can be bothersome and sometimes painful. In earlier studies, impairment of health-related quality of life was evident in IBD, especially when the disease was active. In addition to the physical symptoms, the mental state and social support were also found to affect HRQoL. Data about the impact of demographic characteristics or comorbidity of the patients on HRQoL are partly controversial.

HRQoL can be measured by using generic or disease-specific tools. Generic instruments can be used for comparing health status among patients in different health states, conditions and diseases. However, these instruments do not focus specifically on the issues relevant to a particular disease, as they were developed for general populations. Disease-specific tools may be more responsive to changes within a specific condition.

The disease-specific Inflammatory Bowel Disease Questionnaire (IBDQ) used in this study has been utilized in many earlier surveys with smaller patient samples. In contrast, data about the feasibility of using the generic 15D tool in IBD are scarce. The aims of this study were to compare HRQoL, the frequency of symptoms, and the arrangement of therapy of Finnish IBD patients with those of European IBD patients. The health-related quality of life in Finnish IBD patients using both the IBDQ and 15D instruments was also examined. Furthermore, comorbidity of IBD patients and influence of comorbidity on HRQoL were evaluated.

Patients and methods: The study questionnaire was mailed to 3852 adult (over 18 years of age) members of the Crohn's and Colitis Association of Finland in September 2006, and to an additional 1490 adult patients selected from the Social Insurance Institution register of Finland in February 2008. In study I, the differences in the diagnosis of IBD, current and previous therapies, frequency of IBD symptoms, and impact of symptoms on HRQoL of Finnish patients were compared with those of patients who participated in an earlier European study that comprised 5576 IBD patients from seven countries. Study II evaluated the disease-specific IBDQ scores in Finnish IBD patients. In study III, the generic 15D scores of IBD patients were compared with scores of a gender and age matched general population sample obtained from two national health surveys. Moreover, the 15D scores were compared with the IBDQ scores to evaluate the feasibility of 15D as a HRQoL tool for IBD. In study IV, two age, gender, and hospital district matched control subjects for each participant were selected from the Social Insurance Institution register for a comparison of comorbidity between IBD patients and the general population. Data of other chronic diseases were obtained from the Social Insurance Institution's reimbursement register.

Results: The response rate was 57%. Of these patients, 37% reported that they suffered from disturbing IBD symptoms weekly. In 17% of the patients, the symptoms greatly affected their ability to enjoy leisure activities, and 14% stated that these symtoms greatly

affected their capacity to work. Despite that, the great majority (93%) of patients expressed satisfaction with their current treatment and only 1.4% were very dissatisfied.

43% of the Crohn's disease (CD) patients had undergone surgery, whereas the percentage was 12% for ulcerative colitis (UC). Rates of surgery were lower than in the previous European survey. Over a quarter of operated patients reported postoperative complications in both surveys.

The IBDQ scores ranged from 43 to 224, whereas the possible range is 32 to 224. The mean total score was 163, and disease activity was the most strongly correlated factor with HRQoL. Older age, comorbid diseases, and female gender were also related to impairment of HRQoL. Lower HRQoL scores were also seen in newly-diagnosed patients and in those with a history of surgery, especially after stoma or ileal pouch-anal anastomosis (IPAA) operation.

The range of 15D scores was 0.30-1.00, with a mean of 0.87. As found with the IBDQ, disease activity was strongly correlated with the score, but not even those who reported infrequent symptoms could reach the 15D level of the control group. Sex of the patient or disease type had no significant impact on the score, but older age and a history of surgery were related to lower scores. Newly-diagnosed patients and patients with a long-lasting disease had lower scores than average after adjusting for age. The 15D tool appeared to be a feasible and easy-to-use instrument to assess HRQoL for IBD, and the 15D scores were strongly correlated with the IBDQ scores.

Comorbidity with other chronic diseases was found in 29% of IBD patients. Connective tissue diseases, asthma and chronic obstructive pulmonary diseases, pernicious anaemia, and coronary heart disease were significantly increased among patients with IBD. Females with IBD appeared to be especially at increased risk of CHD with a 1.6-fold prevalence to that of their peers ($p=0.014$), and those who reported weekly symptoms had a higher risk of having other chronic diseases in addition to IBD. Comorbidity impaired HRQoL as measured by using both the generic and disease-specific tools.

Conclusions: IBD had a considerable impact of the daily life of the patients. Symptoms that affected leisure activities, work, and HRQoL were common in IBD. Disease activity was the most important factor related to HRQoL, and older age, comorbidity, and female sex also impaired HRQoL. Newly-diagnosed patients and those with a history of surgery, especially for stoma or IPAA operation, had low HRQoL scores.

The risk for many other chronic diseases, such as CHD, connective tissue diseases, asthma and chronic obstructive pulmonary diseases was increased with IBD. The increased prevalence of CHD in IBD predisposes to more efficacious management of other possible underlying cardiovascular risk factors in addition to the inflammatory activity of IBD. The increased risk for preterm cardiovascular disease should be borne in mind especially in females.

The burden of IBD symptoms on various aspects of general well-being was most marked in those patients with the active disease. However, patients with inactive disease may also have impaired HRQoL, and the impact of the chronic disease on their daily lives may be remarkable. An understanding of predictors of HRQoL will help to recognise patients needing special support.

1 Introduction

The primary aim of medical care is to improve or maintain the overall functional capacity and the general health of patients. The success of a treatment has been traditionally measured by biomedical or clinical end points such as survival, response rates, time to progression, relapse or treatment failure, mortality, morbidity and duration of hospital stay (Sajid 2008).

Edwards and Truelove were probably the first to include a measurement of "invalidism being experienced by the surviving members" in their study on the course and prognosis of ulcerative colitis. In their study, 88% of the patients reported living entirely or essentially normal lives in spite of their disease and the prerequisite hospital visits (Edwards and Truelove 1963). During the last decades, the measurement of health-related quality of life (HRQoL) has become an important outcome in treatment studies in addition to being a factor in health policy decisions (Garratt *et al* 2002). Chronic diseases, which include inflammatory bowel disease (IBD), were found to have a marked impact on HRQoL, especially when frequent symptoms or complications exist (Irvine *et al* 1994, Mili *et al* 2003, Wändell 2005).

Although numerous instruments for HRQoL evaluation have been developed, there is no gold standard for HRQoL. The World Health Organization (WHO) defined HRQoL as:

> *"Individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment"*.
>
> WHO 1997

Having a chronic disease influences HRQoL in many ways. IBDs are chronic diseases that are characterized by remission and relapse periods. Patients often have bothersome symptoms that affect their daily lives, and there is also a risk of having to undergo surgery or having a malignancy. The HRQoL of IBD patients has been surveyed earlier in many studies. However, little is known about the overall quality of life of Finnish IBD patients, or about the impacts of IBD symptoms, comorbidities and given therapies on their daily lives.

This thesis investigated the HRQoL for a large cohort of Finnish IBD patients by using a disease-specific inflammatory bowel disease questionnaire (IBDQ) and a generic 15D questionnaire. The former is used in many earlier IBD studies throughout the world, but to the best of the author's knowledge the latter has not been used in specific IBD studies before. Another aim was to evaluate factors that affect HRQoL in patients with IBD, and to survey comorbidities and their impacts on HRQoL of IBD patients.

2 Review of the literature

Inflammatory bowel diseases, namely Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the gastrointestinal track. The first description of IBD as a separate entity from epidemic dysentery was made by the British physician Samuel Wilks in 1859. In the same year, he also described a case report entitled "Morbid appearances in the intestine of Miss Bankes" in the London Medical Gazette, a case resembling ileocaecal CD (Kirsner 1988). CD was formerly called regional enteritis or terminal ileitis, and is named after Dr. Burrill B. Crohn, who described the disease along with his colleagues Ginzburg and Oppenheimer in 1932 (Crohn *et al* 1932).

2.1 Aetiopathogenesis

2.1.1 Aetiology and pathogenesis

Although the knowledge of immunological mechanisms has increased during the past years, the aetiology and pathogenesis of IBD remains incompletely understood. The most widely accepted hypothesis is that the damage to the bowel mucosa occurs as a result of a dysregulated immune response to multiple mucosal antigens comprised within the constituents of the normal intestinal flora (Baumgart and Carding 2007, Brown and Mayer 2007). Dysbiosis of mucosa-associated intestinal microbiota is one of the major characteristics in IBD (Ott *et al* 2004, Tamboli *et al* 2004, Manichahn *et al* 2006, Rehman *et al* 2010) but its contribution to disease pathogenesis has been controversial (Ott *et al* 2004, Gophna *et al* 2006, Ott *et al* 2008, Nell *et al* 2010).

Intestinal microvascular ischaemia has also been suggested to play a role in the pathogenesis of IBD (Wakefield *et al* 1989, Maconi *et al* 1996, van Oostayen *et al* 1994). An inverse association between appendectomy and UC has been reported in many studies, whereas appendectomy has a positive correlation with CD. The mechanism is unknown, but the appendix may have a role in the mucosal immune system (Koutroubakis and Vlachonikolis 2000).

2.1.2 Genetics

A significant proportion of IBD patients have a positive family history in up to 22% of cases in population-based studies (Gaya *et al* 2006, Ben-Horin *et al* 2009). Moreover, for those IBD patients diagnosed at younger than 20 years of age, over one-third were found to have other family members with IBD (Farmer 1989). The onset of disease in familial IBD cases often occurs at younger age than in sporadic cases (Yang *et al* 1993, Polito *et al* 1996).

In recent years, advances on genome-wide association studies and linkage analysis methods have aided the understanding of the genetics of IBD, as more than 30 IBD susceptible loci have been found (Ishihara *et al* 2009). The findings indicate the polygenic aetiology of CD and UC (Gaya *et al* 2006). The first IBD susceptible gene found was the nucleotide oligomerisation domain 2 (NOD2). This was previously known as the caspase activated recruitment domain protein 15 (CARD15) and is located in chromosome 16 (Hampe *et al* 2001, Hugot *et al* 2001, Ogura *et al* 2001). NOD2/CARD15 mutation has been associated mainly with CD, especially when ileal involvement, fistulizing or stricturing disease phenotype, and/or familially occurring CD are present (Ahmad *et al* 2002, Lesage *et al* 2002, Radlmayr *et al* 2002, Heliö *et al* 2003). In the initial study by Hugot *et al*, allelic variants of the CARD15 gene were found to be present in 43% of patients with CD (Hugot *et al* 1996). However, since that study evidence of ethnic variation in the contribution of the gene has become evident. In Northern Europe, Asia, Ireland and Scotland the contribution of the gene to CD susceptibility is much lower than elsewhere in Europe (Heliö *et al* 2003, Gaya *et al* 2006), and in Finland the allelic frequency in CD patients is only about 5% (Heliö *et al* 2003).

Recently, linkage analyses have drawn the attention of researchers to the IBD3 region (major histocompatibility complex) of chromosome 6p, the IBD5 locus in chromosome 5 (5q31-33) and CARD4 gene in chromosome 7 (7p14) (Gaya *et al* 2006).

2.1.3 Environmental factors

Genetics alone is insufficient to explain the development of IBD. Several environmental triggers have been investigated, and no single factor has been found to be responsible for the development of IBD. Agents that break the mucosal barrier of the intestine such as nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and viral and bacterial infections, have been identified as triggers of IBD (Mayer 2010). Smoking is a risk factor for the development of CD, and is associated with a more active disease, whereas in UC, the effect of smoking seems to be protective (Calkins 1989, Russel *et al* 1998). Stress is not clearly linked to the development of IBD, but it can alter the host immune response or gut flora thus predisposing the subject to the disease (Hunter 2008, Levenstein 2008). A high linoleic acid intake has recently been associated with increased risk of UC. An estimated 30% of cases could be attributed to having dietary intakes higher than the lowest quartile of linoleic acid intake (The IBD in EPIC Study Investigators 2009). Moreover, vitamin D3 has very recently been shown to modify T-cell proliferation and increase IL-6 levels in CD patients (Bendix-Struve *et al* 2010), and vitamin D3 levels have been found to be lower in CD patients than in controls (McCarthy *et al* 2005).

2.1.4 Immune response

The mechanisms responsible of maintaining oral tolerance to microbes and food-derived antigens in a healthy gut are still incompletely understood. The response of a defective

mucosal immune system to mucosal microflora and other luminal antigens in IBD lead to damage and increased permeability of the bowel mucosa (Baumgart and Carding 2007).

There are two basic components to the immune response: the innate and the adaptive response. The innate immunity, which is responsible for the early initial immune response, is more primitive and lacks the specificity and the ability to augment responses upon reinfection. In the intestine, the innate immunity includes the epithelial barrier and phagocytic cells within the lamina propria (macrophages, dendritic cells, and neutrophils). The incidence of IBD is increased in patients with genetic defects in the innate immunology (Dieckgraefe and Korzenik 2002). The expression of α-defensins is needed for prevention of microbial invasion through the intestinal mucosa, and in ileal CD it is lower than in CD patients with unaffected ileum or the ileum of healthy controls (Wehkamp *et al* 2007).

The adaptive immunity, although slower than the innate immunity, complements the immune system and is characterized by specificity and memory. The adaptive immune system is mostly based on T- and B lymphocytes that express antigen receptors on their surfaces (Mayer 2010). Current evidence indicates that defective T-cell apoptosis and impairment of intestinal epithelial barrier play crucial roles in the pathogenesis of IBD (Dignass *et al* 2004). Without the appropriate control of T-cell proliferation and death during an immune response, accumulation of T-cells and intestinal inflammation may occur.

Recently, proinflammatory Th17 cytokines, such as IL-17, IL-22, and IL-23, have been found to play crucial roles in intestinal protection and homeostasis by recruiting neutrophils and macrophages at infected tissues (Shen and Durum 2010).

Toll-like receptors (TLRs) recognise specific microbial components and trigger innate and adaptive antimicrobial responses. In IBD, changes in TLR expression have been found, which leads to the impairment of the elimination of microbes, and also to chronic inflammation (Baumgart and Carding 2007).

2.2 Epidemiology

The peak incidence of IBD occurs between 16-26 years of age (Vind *et al* 2006) and in CD, a slight predominance of females can be seen (Loftus 2004, Vind *et al* 2006).

In many epidemiological studies, a north-south gradient with higher incidence of IBD in northern countries and even within southern and northern parts of the United States, exists (Loftus 2004, Sonnenberg *et al* 1991). A Norwegian study reported that the incidence of IBD was higher in municipalities inhabited by people with the highest level of education and in urban municipalities (Aamodt *et al* 2008). There are also ethnic differences in incidence and prevalence of IBD. The incidence of UC is 3 to 5 times higher in Jews than in non-Jews, which implicates their genetic susceptibility to the disease. Ashkenazi Jews in Israel have a lower incidence of UC than those living in the United States or Northern Europe, which suggests that environmental factors also play an

important role in the pathogenesis of IBD (Niv *et al* 2000). In North America, the prevalence of CD is higher in white individuals and African-American individuals than in Hispanic or Asian people, and differences in disease location and extraintestinal disease complications between ethnic groups have also been observed (Kurata *et al* 1992, Nguyen *et al* 2006). In South Africa, the incidence of IBD in the coloured population is markedly lower than in whites (Wright *et al* 1986). Although IBD incidence in Western countries shows stabilization or decline, rates of IBD continue to rise in many Asian countries (Al-Ghamdi *et al* 2004, Leong *et al* 2004, Asakura *et al* 2009).

A population-based study conducted in Olmsted County, Minnesota, found that the incidence rates of CD and UC increased after 1940, but have remained stable since the 1980's. Today, the prevalence of UC is decreasing, whereas that of CD is increasing due to earlier age of onset and low mortality (Loftus *et al* 2007). Another population-based study reported, that the incidence of CD in Sweden increased until the 1990's, but has been decreasing since 1996 (Lapidus 2006). In Denmark, increasing incidences of both UC and CD have been observed (Vind *et al* 2006). A recently published study of IBD incidence in Pirkanmaa county in Finland in 1986-1999 showed an increase of annual incidence of IBD from 19.5 to 29.2 per 100 000 inhabitants with the increase observed for both UC and CD. The prevalences were 291/100 000 for UC and 124/100 000 for CD (Manninen *et al* 2010). The highest prevalence of CD reported, 319/100 000, was in the province of Nova Scotia, Canada (Bernstein *et al* 2006). The incidence of IBD in children is increasing in many countries (Kolek *et al* 2004, Turunen *et al* 2006, Malaty *et al* 2010). In 2009, the register of the Social Insurance Institution in Finland comprised 33 445 individuals who were eligible for reimbursement for their IBD medication, which equals a prevalence of about 620/100 000 (Statistical Yearbook of the Social Insurance Institution 2010).

2.3 Diagnosis and natural history of IBD

No single specific test for diagnosing IBD is available. Lennard-Jones and Shivananda have defined widely accepted macroscopic and microscopic criteria for diagnosing IBD (Lennard-Jones and Shivananda 1997). Clinical evaluation with a combination of endoscopic, histological, biochemical and sometimes radiological investigations are needed to confirm the diagnosis (Van Assche *et al* 2010a). A Working Party of the 2005 Montreal World Congress of Gastroenterology introduced a classification of IBD, and provided recommendations for clinical classification in practice (Silverberg *et al* 2005). The classification for CD was a modification of the earlier Vienna classification (Gasche *et al* 1998). UC and CD can most often be differentiated by their clinical characteristics. The term "colitis yet to be classified" describes a situation where definitive distinction between UC, CD and other causes of colitis cannot be made after appropriate diagnostic tests (Satsangi *et al* 2006). "Indeterminate colitis" refers to pathological-anatomical diagnosis, which is made usually from a colectomy specimen that has overlapping features of both UC and CD (Price 1978, Satsangi *et al* 2006). In five years follow-up, change of

diagnosis occurred in 9% of the patients originally classified as UC, CD, unclassified colitis or possible IBD. A change to non-IBD was more frequent than change between UC and CD (Henriksen *et al* 2006b).

2.3.1 Clinical presentation

The most pronounced symptoms of UC are loose stools or diarrhoea, which are almost invariably associated with rectal bleeding (Lennard-Jones and Shivananda 1997, Stange *et al* 2008). Patients with the active disease also present with rectal urgency, tenesmi, passage of mucopurulent exudates, crampy abdominal pain, and nocturnal and postprandial defaecation. Constipation or feeling of incomplete evacuation, usually with visible blood in the stools, can also occur in active colitis (Rao *et al* 1988). The onset of UC is often insidious. Systemic symptoms, such as weight loss, fever, tachycardia, nausea and vomiting, are features of severe attack (Baumgart and Sandborn 2007).

Clinical presentation and symptoms in CD depend on disease severity and location. Chronic diarrhoea is the most common symptom that occurs in up to 85% of patients (Nikolaus and Schreiber 2007). Abdominal pain presents in 70% and weight loss in 60% of patients before diagnosis. Blood and mucus in the stools are found less frequently than in UC, but are reported for between 40 and 50% of sufferers (Lennard-Jones and Shivananda 1997). In population-based studies, fistulas occur in about 20% of CD patients and the cumulative incidence increases with duration of the disease (Schwartz *et al* 2002).

As UC is limited to the colon, CD can involve any part of the gastrointestinal tract, most often the ileum and the colon, however (Cosnes *et al* 2002, Silverberg *et al* 2005, Stange *et al* 2008). UC affects the rectum and a variable extent of the colon in continuity. The Montreal Working Group suggests a classification of UC into proctitis, left-sided colitis and extensive colitis (beyond the splenic flexure) and also takes into account disease behaviour and age at diagnosis in addition to disease location (Silverberg *et al* 2005). In a US study, 28% of the patients had proctitis, 25% left-sided colitis and 47% extensive colitis (Loftus *et al* 2000). The extent of UC influences the management and frequency of surveillance of patients (Katsanos *et al* 2007, Stange *et al* 2008). However, the extent of the disease is not a fixed parameter and can change over time. Proximal extension of UC has been observed in up to 53% of patients with a left-sided UC or proctitis (Langholtz *et al* 1996, Moum *et al* 1999). Infrequently, appendiceal skip lesions and backwash ileitis are seen in UC (Ladefoged *et al* 2005, Haskell *et al* 2005).

2.3.2 Clinical course

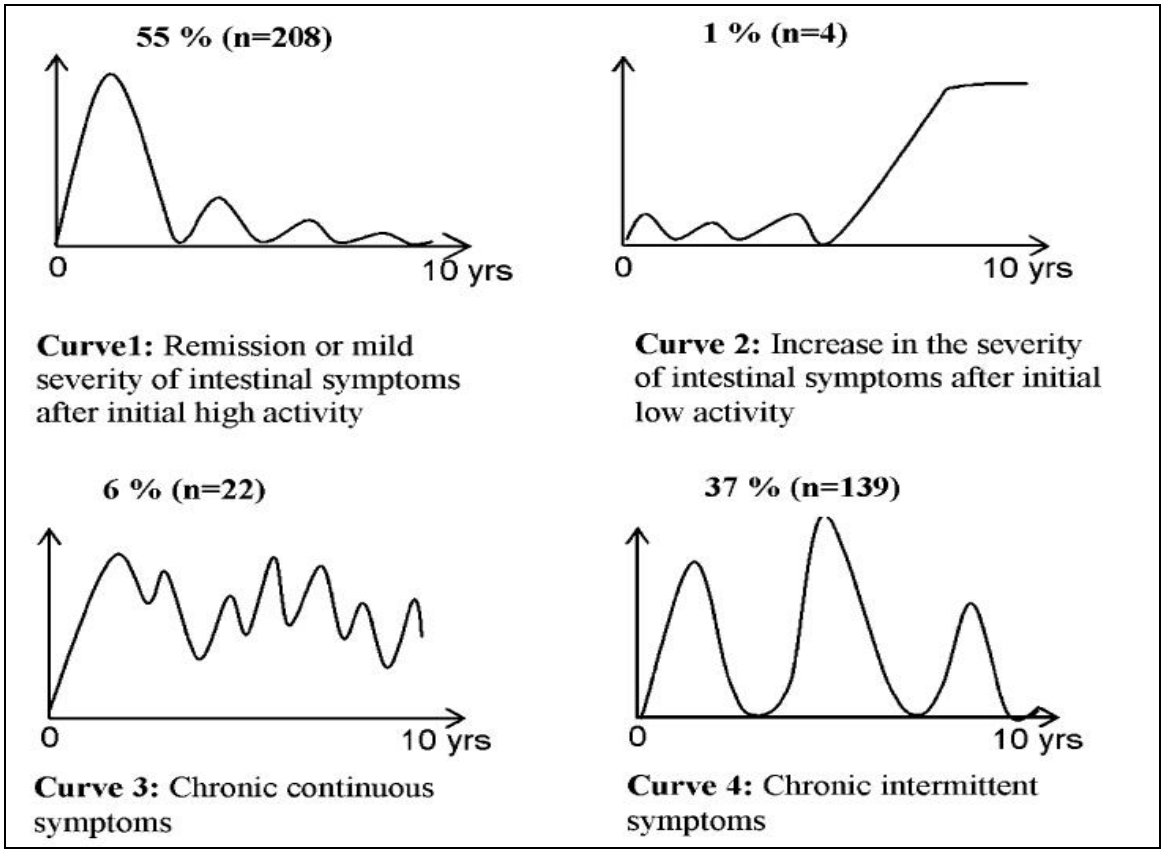
IBD primarily presents at late adolescence or early adulthood and affects both sexes (Loftus 2004, Stange *et al* 2008). The disease is characterized by chronic inflammation and typically has a relapsing and remitting course (Friedman and Blumberg 2008).

In CD, 80% of the patients will experience at least one relapse during a 10-year follow-up (Wolters *et al* 2006a) and 60% of the patients will develop a stricturing or penetrating complication of the disease in the long run (Cosnes *et al* 2002). Patients with small bowel involvement are especially prone to stricturing complications and those with perianal lesions to penetrating complications (Cosnes *et al* 2002). Predictors of progressive disease are age younger than 40 years, perianal disease, and the need for steroids (Beaugerie *et al* 2006).

In UC, a relapsing disease has been reported in over 80% of patients, but some other studies found that nearly half (48%) had stayed in remission for years (Solberg *et al* 2009). Figure 1 shows the different course patterns of UC (Solberg *et al* 2009). A decrease in symptoms has been observed in 59% of patients in a five year follow-up (Henriksen *et al* 2006a), and in a large Norwegian study, 40% of UC patients had been in remission for the last five years of a 10-year follow-up after diagnosis (Solberg *et al* 2007).

No significant increase in mortality has been observed for UC, whereas for CD, there is excess mortality from gastrointestinal causes and, in some studies, from cancer (Masala *et al* 2004, Wolters *et al* 2006b, Höie *et al* 2007, Solberg *et al* 2009).

Figure 1. Different courses of ulcerative colitis in ten years follow-up.
Figure from: Solberg *et al*. Scand J Gastroenterol 2009;44:431-440.



2.3.3 Extraintestinal manifestations of IBD

The most important extraintestinal manifestations of IBD include arthropathies (peripheral and axial), cutaneous manifestations (erythema nodosum, pyoderma gangrenosum, Sweet's syndrome), ocular manifestations (uveitis, episcleritis) and hepatobiliary manifestations (primary sclerosing cholangitis). Peripheral arthritis, erythema nodosum, oral aphthous ulcers and episcleritis are related to IBD activity, whereas pyoderma gangrenosum, uveitis, spondylathropathy and primary sclerosing cholangitis are independent of it (Van Assche *et al* 2010b, Biancone *et al* 2008).

The most common extraintestinal manifestations are inflammatory arthropathies with a prevalence of between 10 to 20%. Radiological evidence of sacroilitis can be detected in up to 25% of the patients, but clinical ankylosing spondylitis, as defined by accepted criteria, can be diagnosed in 3 to 10% (Bernstein *et al* 2001a, De Vos 2004). Non-inflammatory joint pain, i.e. joint pain without underlying arthrosis or arthritis, was reported by 16% of IBD patients (22% in CD) with no association to the extent of the disease, medication, surgery or markers of systemic inflammation (Palm *et al* 2005).
Primary sclerosing cholangitis (PSC) markedly increases risk for cholangiocarcinoma and colon cancer (MacFaul and Chapman 2004). The incidence of PSC is up to 16 in 100 000 in the general population, and over three quarters of PSC patients have also been diagnosed with IBD (Lindqvist *et al* 2010). On the other hand, PSC affects up to 5% of IBD patients (Saich and Chapman 2008). Currently, PSC is the most common indication for liver transplantation in the Nordic countries (www.scandiatransplant.org).

IBD has also been found to be associated with increased risk of osteoporosis and osteopenia, nephrolithiasis, amyloidosis, idiopathic pancreatitis, myocarditis and pleuropericarditis (Danese *et al* 2005).

2.3.4 Endoscopic, radiological and laboratory examinations

2.3.4.1 Endoscopy

Ileocolonoscopy, and systematic mucosal biopsies from each anatomic segment should be performed to establish the diagnosis of IBD. A minimum of two biopsy samples from each of five sites of the colon and the ileum should be obtained for a reliable diagnosis of IBD (Van Assche *et al* 2010a).

Endoscopic appearance is useful in differentiating UC from CD. UC typically presents with continuous, uniform inflammation that extends proximally from the rectum. The inflammation is normally limited to the colon, but occasionally a "backwash" ileitis occurs in total colitis. Rectal sparing has been described in children prior to treatment, and in adults following topical or systemic therapy for UC (Kim *et al* 1999, Rajwal *et al* 2004). The endoscopic features of CD are discontinuous involvement, anal lesions and cobblestone appearance of the ileum. The inflammation can involve any part of the

gastrointestinal tract, and the rectum can be spared. Small, deep aphthous lesions or longitudinal, polygonal ulcerations occur (Nikolaus and Schreiber 2007).

Colonoscopy is used for diagnosis, and also for follow-up of IBD patients. Chromoendoscopy improves detection of pre-malignant and malignant mucosal lesions (Thorlacius and Toth 2007). Oesophagogastroduodenoscopy (OEGD) is recommended for both CD and UC patients with upper gastrointestinal symptoms. OEGD can be useful in patients with unclassified colitis, as focal active gastritis in the absence of ulceration may be a CD feature (Van Assche *et al* 2010a, Stange *et al* 2008). Formerly, only radiographical techniques were available for examinations of the entire small bowel. In recent years, new radiation-free techniques for small bowel examinations have been introduced. Small bowel wireless capsule endoscopy (WCE) serves in making a diagnosis and is used for assessing the severity of small bowel CD, but is contraindicated if suspected or documented intestinal strictures exist (Leighton *et al* 2007). Double-balloon enteroscopy (DBE) is a novel technique that enables endoscopic examination of the entire small bowel. The scope can be inserted either by oral or anal route (Yamamoto *et al* 2001).

2.3.4.2 Radiological techniques

Radiological techniques are mainly used for the examination of the small bowel and extramural complications of IBD. The gold standard for small bowel examination has traditionally been small bowel barium examination (SBE), with either by using an enteroclysis or a small-bowel follow-through. As SBE is invasive and requires ionizing radiation, it is not suitable for follow-up (Horsthuis *et al* 2007). Computed tomography (CT) and magnetic resonance imaging (MRI) are accurate methods for examining extramural complications of IBD, although CT can not be considered suitable for repeat use because of its associated radiation burden. MRI is more suitable for fistula imaging because of its high contrast resolution (Horsthuis *et al* 2007). MRI enteroclysis is superior to conventional SBE in imaging of small bowel lesions in CD (Rieber *et al* 2000). However, as superficial lesions are not accurately visualized with CT or MRI enteroclysis, WCE is preferred in examining inflammatory lesions especially in the jejunum (Gölder *et al* 2006). In the hands of an experienced operator, abdominal ultrasound can reveal small bowel or colonic inflammation in 80-90%, though this is unspecific. It can also be used for detecting fistulas and abscesses (Parente *et al* 2003).

2.3.4.3 Laboratory findings

Initial laboratory investigations of IBD should include a full blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatinine, electrolytes and liver enzymes. Microbiological testing for infectious enteritis including clostridium difficile toxin is needed for differential diagnosis. Anaemia and thrombocytosis are common in the blood count of patients with active IBD (Stange *et al* 2008). Especially in CD, CRP

correlates with disease activity (Vermeire *et al* 2004) and it helps to identify those UC patients with severe exacerbation that needs colectomy (Travis *et al* 1996). Low serum protein or low serum albumin is indicative of protein loss or malabsorption (Nikolaus and Schreiber 2007). Faecal calprotectin can be used for monitoring disease activity, but is not specific for IBD (Konikoff and Denson 2006, Sipponen *et al* 2008).

2.3.4.4 Histology

Histological examination of biopsies taken from the colon and ileum are required for the diagnosis of IBD. In the initial ileocolonoscopy examination, multiple mucosal biopsies should be taken from each segment of the colon (right, transverse, left, sigmoid colon and the rectum) and the ileum. Histology helps in distinguishing between UC and CD, and between IBD and other inflammatory disorders of the gastrointestinal tract (Van Assche *et al* 2010a).

Typical microscopic features of CD include focal or patchy inflammation with granulomas, crypt architectural irregularity, increased basal cellularity (mainly plasmacytes and lymphocytes), erosions, and mucin depletion. In ileal biopsies, the same features, and also irregular villous architecture can be seen. Crypt atrophy is more pronounced in UC. Basal plasmacytosis, mucosal atrophy and crypt epithelial neutrophils are also seen. Inflammation in UC is typically continuous with a decreasing gradient of inflammation from the distal to the proximal colon. Basal plasmacytosis decreases and can disappear during treatment (Jenkins *et al* 1997, Stange *et al* 2008, Van Assche *et al* 2010a).

2.3.5 Assessment of disease activity

A global measurement of IBD activity that comprises clinical, endoscopic, biochemical and pathological features is not available (Sostegni *et al* 2003) but activity can be measured by endoscopic or clinical activity scores. The most commonly used clinical activity score in CD studies is the Crohn's disease activity index (CDAI). The CDAI comprises eight clinical variables, which are: the number of liquid stools, abdominal pain, general well-being, extraintestinal complications, the use of antidiarrhoeal drugs, abdominal mass, hematocrit, and body weight. The CDAI scores range from 0 to approximately 600. The limit between remission and active disease is CDAI 150 and the cut-off value between active and severe disease is 450 points (Sostegni *et al* 2003). Another widely used clinical activity index for CD is the Harvey Bradshaw index, which is based on five variables, namely: the number of liquid stools, abdominal pain, general wellbeing, extraintestinal manifestations and abdominal mass (Harvey and Bradshaw 1980). A score of less than five in the Harvey Bradshaw index is usually the limit for clinical remission (Tibble *et al* 2000). As patients with fistulising disease may score very low in the CDAI and the Harvey Bradshaw indices, the Perianal Crohn's disease Activity Index (PDAI) was introduced. The PDAI includes five items: discharge, pain, restriction

of sexual activity, type of perianal disease, and degree of duration. The PDAI is considered at present the gold standard for evaluating the severity of perianal disease (Irvine *et al* 1995, Sostegni *et al* 2003).

Endoscopic activity in CD can be measured against a Crohn's disease endoscopic index of severity (CDEIS) that ranges from 0 to 44 according to mucosal lesions present and distribution of the disease (Mary *et al* 1989). The scoring system is time-consuming and requires an analogue scale transformation that makes it unsuitable for everyday clinical practice (Sostegni *et al* 2003). It also correlates poorly with clinical activity (Cellier *et al* 1994). Simple endoscopic score for Crohn's disease (SES-CD) is a simpler assessment that is based on four endoscopic variables scored in five endoscopic segments, which yields scores ranging from 0 to 60 (Daperno *et al* 2004). For postsurgical disease activity evaluation, the Rutgeert's score is the gold standard (Sostegni *et al* 2003).

The most commonly used activity indices for UC are modifications of Truelove and Witt's criteria, such as the Lichtiger score and the Mayo score (Truelove and Witts 1955, Lichtiger *et al* 1994). These activity indices include some or all of the following items: stool frequency and form, urgency/incontinence, nocturnal diarrhoea, use of anti-diarrhoeal medications, blood per rectum, abdominal pain, well-being, extraintestinal symptoms, rectal prolapse, fever, laboratory tests, physician's assessment, anorexia, and nausea/vomiting (Turner *et al* 2009). The Mayo Score is the most commonly used index that combines both endoscopical and clinical findings. It consists of four items with three-point scales for the following: stool frequency, rectal bleeding, findings of flexible sigmoideoscopy, and physician's general assessment. Scores range from 0 to 12 points, and patients in complete remission score 0 points (Schroeder *et al* 1987). Clinical improvement is usually defined as a decrease from baseline of the score ≥ 3 points. The Mayo Score has not been validated. (D'Haens *et al* 2007). The non-invasive 9-point Mayo score has been found to perform as well as the full Mayo score for assessing clinical response (Lewis *et al* 2008).

2.3.6 Surgery

Indications for colectomy in UC are severe acute colitis that does not respond to therapy, chronically active disease that causes steroid dependency, and dysplasia or cancer of the colon (Andersson and Söderholm 2009). Nowadays, restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the standard care for elective surgery for UC (Travis *et al* 2008). A total abdominal colectomy with an end ileostomy and the rectal stump left behind is a good alternative for patients requiring emergent surgery for UC. In such cases a restorative operation can be performed when the patient has fully recovered (Grucela and Steinhagen 2009). Total colectomy with ileostomy is recommended for individuals with impaired sphincter function, advanced age, significant comorbidities or distal rectal cancer (Cohen *et al* 2005).

Surgery for CD may be necessary for disease-related complications and emergencies, such as perforation or intestinal obstruction. It may also be used for the control of symptoms when medical therapy is not useful or has failed, such as in case of strictures,

fistulas or neoplasia (Penner *et al* 2005, Kiran *et al* 2010). After ileocaecal resection for CD, 52-72% of patients develop a recurrence and 35% have had repeat resection surgery within 10 years follow-up (Rutgeerts *et al* 1984, Cullen *et al* 2007). Smoking is a risk factor for recurrence (Papay *et al* 2010).

The cumulative 10-year colectomy rate for UC is about 10% (Solberg *et al* 2009). The 10-year cumulative surgery rate for CD is higher, 40% (Wolters *et al* 2006a, Solberg *et al* 2007), and within a year from diagnosis, 12% of CD patients will have undergone resection (Vind *et al* 2006). More than three quarters of CD patients will require surgery at some point of their disease (Penner *et al* 2005). In northern Europe, colectomy rates for UC and overall surgery rates for CD are higher than in southern Europe, which suggests a more severe disease course in the north (Wolters *et al* 2006a, Wolters *et al* 2007). Although immunosuppressants have been used more frequently during the last 25 years, no significant decrease in the need of surgery has occurred (Cosnes *et al* 2005, Domènech *et al* 2010). The overall pouch function is good for most patients after IPAA surgery, and the majority of the patients are satisfied with their pouch function (Ferrante *et al* 2008).

However, the functional result of the pouch is not always satisfactory. In a Swedish study that comprised 370 IPAA patients, median bowel frequency was six times per 24 hours and 76% of the patients had to empty the reservoir during the night. In addition, 23% of patients experienced urgency, 12% evacuation difficulties and 17% soiling during the day (Berndtsson *et al* 2007).

Idiopathic inflammation of the pouch mucosa, “pouchitis”, occurs in up to 58% of operated CU patients (Kuisma *et al* 2004, Ferrante *et al* 2008). Patients with associating PSC (Penna *et al* 1996) or ankylosing spondylitis (Kuisma *et al* 2004) are particularly at risk. Chronic pouchitis, stricturing or pouch fistulas can lead to pouch failure and the need for permanent ileostomy in about 5% of the cases (Lepistö *et al* 2002, Ferrante *et al* 2008). However, of 19 patients with chronic pouchitis and impaired HRQoL, over 80% would still undergo IPAA operation again (Turina *et al* 2006).

2.4 Medical therapy

Medical therapy of IBD is designed in conjunction with the patient according to disease activity, location (ileal, ileocolonic, colonic, rectal) and disease behaviour (relapse frequency, response to previous medications, fistulas, strictures, and extraintestinal manifestations). Patients should be encouraged to participate in therapeutic decisions. In some CD patients with a mild disease, no medication can be an option. In contrast, therapy is usually needed for rectal bleeding and urgency occurring often even in mild rectal inflammation for UC (Stange *et al* 2008, Van Assche *et al* 2010a). As smoking cessation is associated with a more benign disease course for CD, and non-smoking patients have higher rates of response to infliximab therapy, smoking cessation should be recommended to all smokers with CD (Cosnes *et al* 2001, Parsi *et al* 2002).

2.4.1 Aminosalicylates

Oral 5-aminosalicylate (5-ASA) containing compounds are the preferred first-line maintenance treatment for UC. The minimal effective dose of oral 5-ASA is around 1 g/day and higher doses up to 2.4 g/day may be more effective in patients with extensive disease. Sulfasalazine is equally effective to mesalazine but has more adverse effects than mesalazine (Travis *et al* 2008).

Mesalazine suppositories or foam enemas (1 g/day) are the preferred initial treatments for mild or moderately active proctitis, and have a better effect than oral mesalazine alone (Gionchetti *et al* 1998). A combination of oral and topical 5-ASA appears to provide further benefit. Mild to moderate, active UC should be initially treated with mesalazine at a dose of >2 g/day, preferably in combination with topical mesalazine. However, oral aminosalicylates alone can induce remission in a minority of patients (Travis *et al* 2008).

The effect of 5-ASA on the induction or maintenance of remission in active ileal or colonic CD is limited (Hanauer and Strömberg 2004). After curative surgery for ileal CD, mesalazine is useful in decreasing the rate and severity of endoscopic recurrences and can be used in low-risk patients (Brignola *et al* 1995).

2.4.2 Corticosteroids

Corticosteroids have been used since the 1950's when Truelove and Witts published their study regarding the positive effect of cortisone therapy in active UC (Truelove and Witts 1955). Corticosteroids are used as a first-line therapy for active IBD, and over 50% of UC patients have an associated remission (Ho *et al* 2006). In comparison, 38% of CD patients had remission for a year after corticosteroid therapy (Ho *et al* 2006). No difference between classic corticosteroids and placebo exists after 6, 12, and 24 months with maintenance therapy for CD (Steinhart *et al* 2003).

Enteric-coated budesonide has a high anti-inflammatory activity combined with low systemic and steroid activity. Moreover, it has fewer systemic side-effects than conventional corticosteroids because of its rapid hepatic conversion to metabolites. In mildly active ileal or ileocaecal CD, it has been found to be beneficial. However, for maintenance therapy that exceeds one year, the relapse rates equal those of placebo (Greenberg *et al* 1994, Greenberg *et al* 1996). Budesonide is less effective than prednisolone, and severely active or extensive ileocaecal or ileal CD should be treated initially with systemic corticosteroids (Dignass *et al* 2010).

2.4.3 Immunomodulators

The immunomodulative medications, thiopurines (azathioprine and 6-mercaptopurine) and methotrexate are recommended for steroid-dependent or steroid-refractory patients (Travis *et al* 2008). Thiopurines are also recommended for the postoperative prophylaxis of complex CD and for the extensive small bowel CD (Dignass *et al* 2010). A study reported

that 53% of patients that received azathioprine for steroid-dependent UC achieved clinical and endoscopic remission after six months, whereas the rate was 21% for those that received mesalazine (Ardizzone *et al* 2006). Thiopurines are effective therapy for inducing remission in active CD (Prefontaine *et al* 2010). In those cases that need rapid induction of remission, thiopurines alone may be insufficient, as the onset of action is slow (Travis *et al* 2008, Dignass *et al* 2010).

Methotrexate is beneficial in inducing remission in active CD at an intramuscular dose of 25 mg weekly, and it is also significantly more effective than placebo in maintaining remission (Feagan *et al* 1995, Patel *et al* 2009). For the present, data on methotrexate for maintenance of remission in UC are few (Travis *et al* 2008).

2.4.4 TNFα blocking agents

Infliximab is an intravenously administered, chimeric anti-tumour necrosis factor (TNF) monoclonal antibody with a potent anti-inflammatory effect. It is indicated for moderate to severe corticosteroid refractory or corticosteroid dependent IBD, or after failure of other immunosuppressive therapy (Dignass *et al* 2010). Infliximab is usually given as an induction regimen at 0, 2, and 6 weeks at a dose of 5 mg/kg, followed by a maintenance regimen of 5 mg/kg every 8 weeks. A dose of 10 mg/kg can be considered for those patients who lose their response after initially responding (Rutgeerts *et al* 2004).

Infliximab is effective for inducing remission and healing endoscopic lesions in active CD. Up to 80% of patients clinically respond and over 30% go into remission (Targan *et al* 1997). In a large multicenter study, 42% of the patients who received systematic maintenance therapy after successful induction therapy were in remission at 1 year follow-up (Hanauer *et al* 2002). Infliximab is also effective in fistulizing CD, and closure of all fistulas appears in up to 50% of patients after three infliximab infusions. The median time to relapse was 12 weeks, which shows the necessity of maintenance therapy for the majority of patients (Present *et al* 1999).

Infliximab is also an effective rescue therapy for patients who experienced an acute severe or moderately severe attack of UC, and it decreases the rate of colectomy significantly in a three months follow-up (Järnerot *et al* 2005). However, only 24% of patients having maintenance therapy were reported to achieve steroid-free remission at 12 months' follow-up (Rutgeerts *et al* 2005).

Adalimumab, a fully human anti-TNFα monoclonal antibody, was shown to be effective for inducing remission in TNFα-naïve CD patients at a dose of 160 mg at week 0 followed by 80 mg at week 2 (Hanauer *et al* 2006). Moreover, 46% of patients were reported to be in remission after one year (Sandborn *et al* 2007). Adalimumab is usually administered subcutaneously every other week at a dose of 40 mg in maintenance therapy. There is also some preliminary evidence that adalimumab is clinically beneficial for about 20% of UC patients who have lost their response or are intolerant to infliximab (Afif *et al* 2009).

2.4.5 Calcineurin inhibitors

Calcineurin inhibitors are an option for a rescue therapy for steroid-refractory UC. Because of their nephrotoxicity, they are recommended for induction therapy for only 3 to 6 months, until slower-acting immunomodulators, such as azathioprine become effective (Travis *et al* 2008).

Intravenous cyclosporine is effective for patients with severe corticosteroid-resistant UC with a seven-day mean length of time to a response (Lichtiger *et al* 1994). Calcineurin inhibitors reduce the short-term colectomy rate, but the relapse risk remains high in the first year after treatment (Cohen *et al* 1999, Moskovitz *et al* 2006).

Tacrolimus may have an effect in the short-term clinical improvement of refractory UC patients. More data are needed to determine the long-term efficacy and safety (Baumgart *et al* 2008). Calcineurin inhibitors are of limited value for CD (Dignass *et al* 2010).

2.4.6 Antibiotics

For mild to moderate flare-up of CD, ciprofloxacin has been found to have similar efficacy to that of 5-ASA with a response rate of 40-50% after 6 weeks of therapy (Colombel *et al* 1999). Metronidazole can be used alone, or in combination with ciprofloxacin. They can be used for the therapy of pouchitis, for which both metronidazole and ciprofloxacin have proved to be beneficial (Pardi and Sandborn 2006). However, antibiotics can not be considered effective in inducing or maintaining remission for UC (Travis *et al* 2008).

2.4.7 Nutritional therapy

Malnutrition, caused by reduced food intake, presence of active inflammation and enteric loss of nutrients, is a common problem with active IBD, especially for CD (Hartman *et al* 2009). IBD is associated with disturbances in body composition, so both bone mineral content and lean body mass are lower than those of healthy subjects. This is most striking for males with CD (Jahnsen *et al* 2003). Enteral nutrition, usually liquid preparations containing aminoacids or whole protein, can be used to induce or maintain clinical remission, and to improve nutritional status and body composition. Nowadays parenteral nutrition is mainly used for treatment of severe malnutrition and as a pre- or postoperative nutritional support, as enteral nutrition is as effective with lower costs and fewer side effects (Hartman *et al* 2009). Elemental or polymeric diets are less effective than corticosteroids in the treatment of active CD (Dignass *et al* 2010). No convincing data on effects of different elimination diets for the treatment of IBD exist (Yamamoto *et al* 2009).

Because of the increased risk for osteoporosis, sufficient intake of calcium and vitamin D is necessary (Ali *et al* 2009). Anaemia is a common finding with IBD, and it should be

treated by optimizing therapy of active IBD, and by administrating oral, or in some cases, intravenous iron supplements (Gisbert and Gomollón 2008).

2.5 Comorbidity

2.5.1 Autoimmune diseases

In a recent population-based study from the US, the risk for ankylosing spondylitis was found to be substantially higher for IBD patients than in the general population with an odds ratio (OR) of up to 7.8. Moreover, prevalences of atopic dermatitis, psoriasis or multiple sclerosis were increased by approximately 1.5-fold. No increased risk for type I diabetes mellitus was observed (Cohen *et al* 2008). The risk for demyelinating diseases has been found to be increased in other surveys, as well (Gupta *et al* 2005). The risk for rheumatoid arthritis is also increased with IBD (OR 1.8-2.7) (Bernstein *et al* 2005, Cohen *et al* 2008). Clustering of many autoimmune diseases in the first-grade relatives of IBD patients has also been observed (Hemminki *et al* 2010).

2.5.2 Pulmonary diseases

A broad spectrum of respiratory symptoms (such as wheeze, cough, dyspnoea and sputum production) and lung diseases have been associated with IBD. The most commonly reported lung diseases are bronchiectasies, acute and chronic bronchitis and asthma (Bernstein *et al* 2005, Black *et al* 2007). Incidences of many pulmonary diseases, such as bronchiectasies, bronchiolitis and interstitial pulmonary disease, are increased in IBD independently of smoking habits or medication (Mahadeva *et al* 2000).

2.5.3 Thromboembolic and vasculatory disease

Many predictors of atherosclerotic disease, such as levels of carotid arterial stiffness, homocysteine, high-sensitivity CRP, and insulin resistance that support the increased risk for early atherosclerosis are evident in IBD (Papa *et al* 2005, Brezenger *et al* 2006, Dagli *et al* 2010). On the other hand, IBD patients with coronary heart disease (CHD) have been found to have lower Framingham risk scores (fewer risk factors) than patients with only CHD (Sappati Biyyani *et al* 2009).

A large population-based study from Manitoba, Canada reported that the risk for ischaemic heart disease was increased in both sexes with CD and with UC, and reported an incidence rate ratio (IRR) of 1.26 (CI 1.11-1.44). Furthermore, an increased risk for cerebrovascular disease was seen in CD (IRR 1.32, CI 1.05-1.66) (Bernstein *et al* 2008).

In another study, increased risk for myocardial ischaemia could be confirmed only in females aged over 40 (hazard ratio 1.6) (Ha *et al* 2009). However, mortality for cardiovascular diseases has not been found to be elevated in IBD patients (Dorn and Sandler 2007).

Coagulation and fibrinolysis, rate of venous thromboembolic complications, which have been shown to be interrelated with inflammation, are also increased with IBD (Danese *et al* 2007). The most common thromboembolic complications are pulmonary embolism and deep vein thrombosis with over a three-fold risk compared to the general population (Miehsler *et al* 2004).

2.5.4 Malignancies

UC has long been known to be associated with increased risk of colorectal cancer (CRC) and the risk increases with a longer duration and with the extent of the disease. More recently, increased risk of CRC has been associated with CD, as well (Bernstein *et al* 2001b). In a meta-analysis, the cumulative probability of CRC in UC was 2% by 10 years, 8% by 20 years and 18% by 30 years of disease duration (Eaden *et al* 2001). In IBD patients, 3% of CRC diagnoses are made coincidentally on pathological specimens after colectomy for other reasons (Kiran *et al* 2010). In a 20 years follow-up study, dysplasia or cancer was detected in 43% of UC patients who attended surveillance colonoscopies. The mortality of all the patients who attended the study was not increased, however. This was probably due to the surveillance program and frequent medical check-ups (Lindberg *et al* 1996). The risk of small bowel carcinoma in CD is increased 40-fold (Jess *et al* 2006).

The risk of hepatobiliary carcinoma is also increased with both UC and CD, and most cases are associated with PSC (Bernstein *et al* 2001b). A study showed that in some patient cohorts cholangiocarcinoma can be found in 50% of PSC patients within one year after the diagnosis (Fevery *et al* 2007).

A large population-based study reported an increased risk of lymphoma in male CD patients (IRR 3.63, CI 1.53-8.62) (Bernstein *et al* 2001b). Lung cancer appears to be increased for CD compared to UC or the general population, probably due to the high prevalence of smoking in CD (Masala *et al* 2004).

2.5.5 Psychiatric conditions

Psychological comorbidity, mainly anxiety and depression, are frequent findings with IBD (Addolorato *et al* 1997, Miehsler *et al* 2008). Both depression and anxiety are found significantly more often for IBD than for control populations, and they are related to frequency of disabling symptoms and also to the nutritional level (Addolorato *et al* 1997). Increased levels of anxiety, depression and distress have been found in inactive IBD patients, as well (Farrokhyar *et al* 2006, Graff *et al* 2009). An Austrian study used a validated questionnaire, which evaluated the need for psychological treatment, and found

that 24% of IBD patients expressed a need for psychosomatic support. The rate was significantly higher than for age matched and sex matched rheumatoid arthritis patients. Inadequate social support and anxiety appeared to increase the need for psychological intervention especially in younger age (Miehsler *et al* 2008).

Higher levels of depression or anxiety at baseline may be related to more frequent relapses of IBD (Mittermaier *et al* 2004). Furthermore, increasing the number of stressful events appeared to increase risk of relapse in previously inactive UC patients after controlling for demographic factors (Bitton *et al* 2003). In another study, short-term stress was not associated with exacerbations for UC patients, but long-term stress was a risk factor for relapses, which emphasizes the biopsychological origin of diseases (Levenstein *et al* 2000). However, some studies found no evidence of impact of psychosocial stress on disease exacerbations. Instead, an increase of physical symptoms led to increased level of psychological disturbance (North *et al* 1991). In some studies, IBD patients with active disease were more likely to use maladaptive, avoidant coping strategies than patients with inactive disease or the general population (Graff *et al* 2009), but in others, no differences in coping strategies were found between inactive and active patients or between patients with CD and UC (Larsson *et al* 2008). Evidence of the effect of cognitive-behavioral treatment for reducing psychological distress and disease-related concerns in IBD patients exists (Mussell *et al* 2003).

2.6 Education level and working capacity

The level of education of young IBD patients in Scotland was similar to their peers although 40/70 (57%) of the patients reported absences of two months or more from school because of their disease, and many reported that their education had been adversely affected by the disease. 6/70 (8.5%) of IBD patients were involuntarily unemployed (Ferguson *et al* 1994). A Norwegian study reported that 11.7% of the patients were unemployed at five years follow-up after diagnosis of IBD, whereas the average unemployment rate in the Norwegian population was 4.1%. A rise in disability pension rates was recorded for CD patients aged 30 to 50 years. Furthermore, CD patients had twice as many sick-leave days as the general population, whereas the rate for UC was only slightly elevated. Unemployment was associated with significantly lower HRQoL scores for UC patients (Bernklev *et al* 2006). The ACT 1 and 2 studies examined the efficacy of infliximab in therapy of UC, as well as the employment status of patients and their HRQoL. At week 30, among the 257 patients who were unemployed at the beginning of the study, a greater percentage of those in remission were employed than of those not in remission (58.8% versus 20.0%, $p<0.05$), and the number fully productive hours worked was greater for those in remission (Reinisch *et al* 2007).

In a study comprising both UC and CD patients with permanent ileostomy, 36% reported that before surgery their illness prevented them from pursuing a career of their choice. After surgery, 64% of the patients had the same job status as held preoperatively,

and 13% worked more and 22% less than before surgery. Moreover, 15% had lost their jobs after surgery, and nearly half of them thought that it was because of the ileostomy (McLeod *et al* 1986).

2.7 Health-related quality of life (HRQoL)

2.7.1 Definition of HRQoL

The WHO's defined health in 1948 as: "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity", which should be considered more as an ideal rather than a reality. The concept of "quality of life" describes the general well-being of an individual or a society. It is distinct from health, but health is one of the parameters most strongly associated with experienced quality of life. Other parameters of quality of life include wealth and employment, environment, education, recreation, leisure time, and social inclusion or exclusion (Flanagan 1978). The relative importance of essential issues related to the quality of life has been studied. In an UK study, respondents most often mentioned relationships with family or relatives (31%), their own health (23%), the health of another person (20%), and finances/standard of living (10%) as the most important issues related to quality of life. Those who reported their health to be impaired, were most likely to mention their own health as the most important issue affecting quality of life (Bowling 1995).

HRQoL indicates the overall effect of a disease on a person's ability to enjoy life. It is a measure of the functional impact of a (chronic) illness and a given therapy on the daily life of an individual, as seen from that individual's viewpoint (Fitzpatrick 1992, Wilson 1995).

Most conceptualistic models of HRQoL include the dimensions of physical, social and role functioning, in addition to mental health and general perceptions of health (Wilson 1995). These dimensions impinge on each other, and they are affected by the patient's personality characteristics, social support, economical support, and non-medical factors, such as political and cultural factors (Fitzpatrick 1992, Wilson 1995).

2.7.2 Applications of quality of life measurement

The need for HRQoL evaluation has arisen to meet the objective of medical therapy to improve patients' general well-being, which is the most important reason for HRQoL measurement (Ebrahim 1995). HRQoL measurement helps to identify the most appropriate choice between different therapies with their benefits and adverse effects (Sajid 2007). On the population level, HRQoL measurement can be used for monitoring population health and changes in it, for evaluating the effects of health and social policies, and for allocating health care resources in relation to need. On an individual level,

HRQoL measurement serves to evaluate the effects of treatment, to describe the nature and severity of a disease, and to assess prognosis (Ebrahim 1995).

HRQoL measurement has become an essential outcome of cost-effectiveness and cost-utility analyses, as well. A quality-adjusted life year (QALY) can be thought as a year of life that is lived at an optimal state of health. If a medical intervention adds 10 years of life, and each of these years is associated with a HRQoL score of 0.7 (of the maximum being 1.0), that medical intervention will result in a gain of seven years (10 x 0.7) of perfect health or QALYs (Muennig 2002). Therefore, HRQoL instruments measure the impact of a treatment on the quality of life without incorporating influence on the length of life, whereas QALY assessment combines both quantity and quality of life into a single value. In addition, the cost of the intervention is integrated into the cost-effectiveness analyses (Raisch 2000). The accepted cost-effectiveness threshold varies across different countries depending on the availability of health-care resources and technology, as well as on general valuations (Ebrahim 1995, Devlin and Parkin 2004).

2.7.3 Assessment of HRQoL

The purpose of the HRQoL instruments is to calculate a score based on a person's perception of his/her quality of life. The HRQoL score is therefore a valuation of life lived in a particular state of health (Muennig 2002). The primary source of information for HRQoL measurement should be the patient him- or herself (Bjordal 2004). HRQoL questionnaires are administered by trained interviewers, proxies or by patients themselves (self-administration). Surrogate respondents can be used to predict results that cannot be obtained directly from the patient, for example, if the patient is too sick to complete the questionnaire (Guyatt *et al* 1993).

2.7.4 Types and structure of HRQoL instruments

There are two main types of HRQoL instruments, generic and disease-specific. Generic instruments can be further divided into two groups: health profiles containing instruments that attempt to measure separately all important aspects of HRQoL, and utility measures comprising instruments that reflect preferences of patients for treatment process and outcome, and yield a single score. The latter can be used for cost-utility analyses (Guyatt *et al* 1993). Some generic instruments have features of both groups. Global HRQoL assessment refers to a simple summary of overall HRQoL by using a visual analogue scale (VAS), which is usually a horizontal line with one end indicating the worst health and the other end the best health, and the respondent indicates the point that best reflects his/her response to the question by placing a mark on the line. A graded scale with a single attribute can also be used. These assessments are easy to perform, but do not identify specific areas of dysfunction (Borgaonkar and Irvine 2000).

A questionnaire usually consists of several questions or items, which can be grouped into domains or dimensions, which measure physical or emotional function, for example.

Answers to questions are usually scored on a scale. The Likert scale is a category scale by which respondents specify their level of agreement to a statement, such as: 1= strongly disagree, 2= disagree, 3= neither disagree nor agree, 4= agree, 5= strongly agree. The questions may have various number of answer options depending on the questionnaire. In some questionnaires, the score is calculated by summing the answers to all the individual items. However, some others use more complex calculations by utilizing preference weights for each question.

2.7.5 Properties of HRQoL instruments

All useful HRQoL measurements must have the prerequisite characteristics that make them useful for the purpose intended (Ebrahim 1995).

First, the instrument must be reliable. The concept of reliability consists of three aspects: test-retest repeatability, inter-observer repeatability, and internal consistency. Internal consistency is a measure of the extent to which the items of the scale are related to each other, i.e. the extent to which they measure consistent underlying concepts (Guyatt *et al* 1993).

Another important characteristic of an instrument is validity. Validity refers to the ability of the instrument to measure a predefined parameter. The criterion validity refers to the ability of an instrument to correspond to results of the criterion standard (i.e. a shorter version of an instrument versus the full-length instrument, "the gold standard"). Face validity is the property of an instrument to appear to test the parameter intended, whereas content validity refers to the extent to which a measure represents all facets of the issue in question. Construct validity is the agreement between HRQoL scale and predefined expectations about how it should behave in different situations, for example, the ability to show similarity among like groups (Guyatt *et al* 1993, Irvine *et al* 1994).

Responsiveness, or sensitivity to change, is the instrument's ability to detect change in HRQoL. The terms "ceiling effect" and "floor effect" are linked with responsiveness. If the ceiling effect of an instrument is high, many patients gain the best score, and for these individuals, the instrument is not capable of detecting any further improvement in HRQoL. Conversely, the floor effect prevents the detection of HRQoL impairment in those subjects with the worst possible scores (Guyatt *et al* 1993, Ebrahim 1995).

A good HRQoL instrument is also feasible for the researcher, acceptable for the patient, interpretable, and useful in providing tools for clinical and political decision making (Sajid *et al* 2007). An adequate validation of the instrument is important prior to its application in clinical practice or research to minimize the risk of missing important observations or focusing on inconsequential problems (Irvine 1996). After these criteria have been taken into account, there are no uniformly 'worst' or 'best' performing instruments. Consequently, the instrument selection should be made by using the characteristics that are considered most relevant to the study (Coons *et al* 2000).

2.7.6 Generic HRQoL instruments

Generic instruments are often preference-based and designed to provide a summary of HRQoL. The questionnaires have been developed by obtaining importance weights of each dimension of the questionnaire, and also by obtaining the values assigned to a particular state of health from a general population sample (Muennig 2002). Their aim is to create a standardized health state descriptive system by choosing the correct dimensions in which health is to be measured and by dividing each dimension into discrete levels that correspond to different health states (Sintonen 1994). Generic instruments can be used for comparing health status among patients with different health states, conditions and diseases. However, as developed for general populations, these instruments do not focus specifically on the impact of a particular condition on HRQoL, and they may be less capable of detecting small but clinically important changes over time or changes related to treatment of a specific disease (Cramer *et al* 2002). Their most important function is to enable comparisons between populations with different diseases, and also comparisons with the general population. Generic instruments are suitable for calculating QALYs for cost-effectiveness analyses of different therapies (Raisch 2000). Properties of the most important standardized generic HRQoL instruments used in IBD are discussed below.

2.7.6.1 Medical Outcomes Study Short-Form

The Medical Outcomes Study Short-Form (SF-36) was designed to study health status in the Medical Outcomes Study. It is suitable to be used in clinical practice and for research, health policy evaluations and general population surveys, and it has been widely used. It has 36 questions, so is relatively fast and easy to use, and can be self-administered or interviewer-administered (Ware and Sherbourne 1992, Brazier *et al* 1992). In a study by Essink-Bot *et al,* SF-36 had superior validity to that of the EuroQoL and the Nottingham Health Profile (Coons *et al* 2000). Abbreviated versions (SF-20 and SF-12) of SF-36 have been developed, but their reliability and validity are slightly lower than those of the SF-36 questionnaire (Stewart *et al* 1988).

2.7.6.2 EuroQoL

The EuroQoL (EQ-5D) comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three answer options, in addition to a VAS that describes the current general health state at a scale from 0 to 100. EQ-5D was developed with the intent of constructing a simple, self-administered instrument that was particularly useful when used alongside with other measures of health status. It can be used for clinical studies, and for population surveys. EQ-5D provides a simple descriptive profile, and a single index value that describes health status. In total 243 health states can be differentiated according to answers to the five items of the questionnaire and the VAS scale (www.euroqol.org). EQ-5D has a good reliability but it has a high ceiling effect, as with many other generic tools (Coons *et al* 2000).

2.7.6.3 Sickness Impact Profile

The Sickness Impact Profile (SIP) is one of the first validated and extensively used health state measures. It is behaviourally based and serves both as an evaluative and as a discriminative measure (Gilson *et al* 1975). SIP comprises 136 items in 12 categories. The minimum score of 0% indicates absence of dysfunction, and 100% maximal dysfunction. High test-retest reliabilities have been reported for SIP. However, its administration is time-consuming (20 to 30 minutes when interviewer-administered). Moreover, the SIP may fail to detect small, but existing differences in HRQoL, or to detect small changes in health after treatment in those patients with mild disease because of its high ceiling effect (Yacavone *et al* 2001).

2.7.6.4 Nottingham Health Profile

The Nottingham Health Profile (NHP) was developed in the UK for being used in epidemiological studies. NHP assesses subjective health by using 38 statements in 6 sections requiring "yes" or "no" for an answer. The score is calculated using weighted values, which yield scores ranging from 0 (no problems) to 100 (maximal problems) for each section. NHP has a high degree of relevance and acceptability to patients and it is simple to complete and score (Yacavone *et al* 2001). In reliability testing it has shown good test-retest correlations (Coons *et al* 2000). Its main disadvantage is a relatively high floor effect which limits its usefulness in the general population (Coons *et al* 2000). The ceiling effect is similar to that of SIP (Yacavone *et al* 2001), and NHP is less sensitive to minor levels of discomfort than SF-36 (Brazier *et al* 1992, Ebrahim 1995).

2.7.6.5 Psychological General Well-Being

The Psychological General Well-Being (PGWB) is a 22-item questionnaire that measures subjective feelings of well-being and distress. Responses are graded on a six-point Likert scale with higher values indicating better well-being. Six dimensional scores (anxiety, depression, general health, positive well-being, self-control, and vitality), comprising three to five items, are calculated. The total score is the sum of the domain scores with a maximum of 110 points. A shorter, 6-item version of PGWB has also been developed, but hitherto it has not been fully validated (Grossi *et al* 2006). Reliability testing has shown tendency of initially low scores to rise and initially high scores to fall in the event of re-testing, which indicates the need for caution in interpreting results in longitudinal studies (Yacavone *et al* 2001).

2.7.6.6 15D

15D is a 15-dimensional, comprehensive instrument that yields both a profile and a single index score measure. 15D is designed to be self-administered, though interviewer or proxy administration can also be used. 15D includes the following dimensions: breathing, mental function, speech (communication), vision, mobility, usual activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, sexual activity, and depression. Each dimension is rated against a five-point scale and the score is calculated by utilizing preference weights obtained from the general population. The maximum score is 1 (no problems on any dimension), and minimum 0 (deceased). 15D has been used in the Finnish National Health Survey 1995/96 and the Health 2000 Survey, thus it provides a large general population sample for comparison studies (Sintonen 2001). With regards to the ceiling and floor effects, 15D is superior to NHP and EQ-5D and equivalent to SF-20 (Sintonen 1994). Responsiveness to change has been found to be roughly comparable between 15D, NHP and SF-20 (Sintonen 2001). Completion rates of 15D questionnaires have generally been 96-100%, and a small number of missing answers can be fairly accurately predicted by regression models with the responses on the other dimensions, age, and gender as explanatory variables. A change of $\geq$0.03 in 15D score can be sensed by an individual (Sintonen 1994). 15D has been used in several conditions, drug evaluations, rehabilitation and treatment studies (www.15d-instrument.net/15d). The mean 15D score was 0.91 for the general population of the Health 2000 Survey. Impairment of 15D scores occurs with increasing age (Saarni *et al* 2006). Two versions of 15D exist for studying children and adolescents; 17D for children aged 8-11 years and 16D for adolescents aged 12-15 years (Apajasalo *et al* 1996a, Apajasalo *et al* 1996b). The most important studies that have used 15D are shown in Tables 1 and 2.

Table 1. Overview of 15D studies

Author and year	*Disease*	*Number of patients*	*Purpose of study*	*15D score*
Stavem 1998	Epilepsy	57	Comparison of different HRQoL tools	0.89
Stavem 1999	Chronic obstructive pulmonary disease	77	Comparison of different HRQoL tools	0.80
Hahl *et al* 2002	Diabetes mellitus	539	Measurement of HRQoL in diabetes, and impact of diabetes-related complications and age on HRQoL	Impairment of HRQoL with increasing age and with diabetic complications
Haapaniemi *et al* 2004	Parkinson's disease	260	Assessment of feasibility of 15D in Parkinson's disease	0.77 (matched controls 0.86)
Dahlberg *et al* 2005	Spinal cord lesion	117	Evaluation of HRQoL	0.78 (matched controls 0.95)
Yildirim 2006	Renal insufficiency	646	Evaluation of HRQoL in renal transplant patients	0.94 (transplantation), 0.57 (haemodialysis), 0.46 (peritoneal dialysis)
Saarni *et al* 2007	Various diseases	6166	Impact of chronic diseases on 15D scores (Health 2000)	0.91 (population)
Gvozdenovic *et al* 2008	Sarcoidosis	81	Comparison of patients with pulmonary and with extrapulmonary sarcoidosis	0.76
Miettola *et al* 2009	Metabolic syndrome	480 (metabolic syndrome 181)	Examination of HRQoL in metabolic syndrome	Significantly lower 15D score in patients with metabolic syndrome
Pirkola *et al* 2009	Anxiety/ depression	6986 (685 with anxiety or depression)	Impact of anxiety or depression disorder on HRQoL	0.91 (no anxiety)/0.89 (anxiety), 0.80 (current depression)
Tikkinen *et al* 2010	Nocturia	3474 (nocturia 1530)	Evaluation of association between frequency of nocturia and HRQoL	0.94 (no nocturia)/0.83 (over two voids per night)
Mattila *et al* 2010	Alexithymia	5090	Assessment of HRQoL in alexithymia	Impairment in all 15D items in alexithymia
Ahola *et al* 2010	Type I diabetes	1023	Impact of diabetes and its complications on HRQoL	0.90 (all), impairment of scores if diabetic complications present

HRQoL = health-related quality of life

Table 2. Overview of intervention studies with 15D

Author and year	*Disease*	*Number of patients*	*Intervention/ therapy*	*Time of follow-up*	*15D score before/ after intervention*
Kauppinen *et al* 2000	Asthma	134	Patient education and supervision for self-management for novel asthmatics	5 years	0.03 points' mprovement of 15D score
Räsänen *et al* 2006	Cataract	219	Cataract surgery	6 months	0.82/0.83
Räsänen *et al* 2007	Various conditions affecting joints	223	Hip and knee replacement surgery	12 months	0.81/0.86 (primary hip arthroplasty), 0.81 (primary knee arthroplasty)
Laas *et al* 2009	Rheumatoid diseases	295	Patients with new referral to clinic of rheumatology	8 months	0.82/0.84
Loponen *et al* 2009	Coronary artery disease	469	Coronary artery bypass surgery (CABG)/percutaneous coronary intervention (PCI)	36 months	0.82/0.86 (CABG, 6 months), 0.83/0.85 (PCI, 6 months)
Salo *et al* 2010	Chronic neck pain	180	Neck strength training	12 months	0.90/0.93
Kantola *et al* 2010	Acute liver failure	90	MARS (molecular adsorbent recirculating system)	median 49 months	0.30/0.70

2.7.7 Disease-specific HRQoL instruments

Specific instruments focus on aspects of health status that are specific to the area of interest, such as a certain disease, condition, function or problem, or a population of patients (Guyatt *et al* 1993). Disease-specific instruments are usually more responsive to changes in evaluation of HRQoL in a specific condition (Irvine *et al* 1994). Clinical trials that evaluate specific therapeutic interventions most often utilize disease-specific HRQoL tools (Yacavone *et al* 2001). Disease-specific HRQoL tools have been developed for numerous diseases and conditions. Several disease-specific tools exist for evaluating HRQoL in IBD, the most important of which are presented below.

2.7.7.1 Inflammatory Bowel Disease Questionnaire

The most commonly used HRQoL instrument in IBD, translated into over 40 languages, is the Inflammatory Bowel Disease Questionnaire (IBDQ) (ip.mcmaster.ca/questionnaires/ questionnaires).

The questionnaire consists of 32 questions rated most important to the HRQoL by IBD patients and their physicians. The questionnaire has four domains: gastrointestinal

symptoms, systemic symptoms, emotional function and social function, with each domain comprising five to 12 items. Responses range from 1 (worst) to 7 (best). The total score ranges from 32 to 224, and is calculated by summing all the answers to the 32 questions. Mean scores per item for each domain (range 1 to 7) can also be calculated. The questionnaire has been validated and it is sensitive to change in IBD patients (Guyatt *et al* 1989). However, systemic function (such as fatigue, sleep, and energy level) is more responsive to change than emotional or social scores. In remission, scores are generally 170 points or more, and a mean decrease in relapse is about 32 points (Irvine *et al* 1994, Cregor *et al* 1997).

Alternative versions of the IBDQ have been developed. A short-form IBDQ (SIBDQ) consists of 10 questions and has been developed for clinical use. It is useful in both UC and CD (Han *et al* 2000). A version designed for stoma patients is also available. The most important surveys utilizing IBDQ are presented in Tables 3 and 4.

2.7.7.2 Rating Form of IBD Patient Concerns

The Rating Form of IBD Patient Concerns (RFIPC) was developed to evaluate disease-related worries and concerns of IBD patients. The questionnaire is self-administered and has 21 items. Items are in the form "Because of your condition, how concerned are you with…?" Patients rate concerns from 0 to 100 on a VAS, and the total score is the mean of all answers (Drossman *et al* 1989). This instrument is well suited to guiding patient education and counselling because of its focus on patient concerns (Yacavone *et al* 2001) but it has also been used in HRQoL studies (Stjernman *et al* 2010).

2.7.7.3 Cleveland Clinic IBD Scale

The Cleveland Clinic IBD Scale was developed for use as a routine management tool for ambulatory IBD patients. It has 47 items, of which 45 are scaled and two require descriptive answers. The questionnaire comprises four categories: functional/economic, social/recreational, affect/life in general, and medical/symptoms. The questionnaire has not yet been fully validated (Yacavone *et al* 2001).

Table 3. Overview of earlier studies with Inflammatory Bowel Disease Questionnaire (IBDQ)

Author and year	*Number of patients*	*Disease*	*Main result*	*Study purpose*
Hjortswang *et al* 2001	276	UC	202 (remission)/ 167 (relapse)	Validation of Swedish version of IBDQ
Casellas *et al* 2001	289	CD 129, UC 160	Disease activity affected HRQoL	Study the influence of IBD on different dimensions of HRQoL
Nordin *et al* 2001	492	CD 161, UC 331	Anxiety and depression impair HRQoL	HRQoL and distress in IBD
Casellas *et al* 2002	354	CD 169, UC 185	CD: mean per item 6.1 (remission/4.2 (active), UC: 6.3 (remission)/4.1 (active)	Impact of health status and socio-demographic factors on HRQoL
Rubin *et al* 2004	409	CD 163, UC 239 IC 7	Lower HRQoL scores for women, in CD and for those under specialist care	HRQoL in established IBD, community-based study
Casellas *et al* 2005a	1156	CD 628, UC 528	Mean per item 6.1 (remission)/ 4.5 (active)	Impairment of HRQoL in IBD
Bernklev *et al* 2004, 2006	497	CD 169, UC 328	CD: 157 (sick leave)/187 (no sick leave), 173 (♀)/186 (♂); UC:174 (sick leave)/192 (no sick leave), 183 (♀)/191 (♂)	Impact of demographic variables, sick leave and unemployment on HRQoL
Stjernman *et al* 2006	448	CD	193 (remission), 161 (active)	Evaluation of validity of IBDQ in Swedish CD patients
Watanabe *et al* 2006	64	UC with IPAA	IBDQ mean 165.7	IBDQ in IPAA patients
Moreno-Jiménez *et al* 2007	120	CD 60, UC 60	Neuroticism impaired all four IBDQ subscores	Influence of personality factors on HRQoL
Gibson *et al* 2007	143	CD	180.6 (CDAI <150), 115.4 (CDAI ≥220)	Impact of disease severity on HRQoL and health-care resource use
Vidal *et al* 2008	147	CD 76, UC 71	Hospital Anxiety and Depression Score was negatively correlated with IBDQ scores	Impact of anxiety and depression on HRQoL
Kuriyama *et al* 2008	331	UC	mean per item 5.9 (disease duration <5 years), 6.0 (≥10years)	Impact of disease duration on HRQoL
Hyphantis *et al* 2010	185	CD 64, UC 121	198.5 (low anxiety), 146.4 (high anxiety)	Impact of psychological distress on HRQoL

CD = Crohn's disease; HRQoL = health-related quality of life; IBD = inflammatory bowel disease; IPAA = ileal pouch-anal anastomosis; UC = ulcerative colitis

Table 4. Overview of earlier treatment or intervention studies with Inflammatory Bowel Disease Questionnaire (IBDQ)

Author and year	*Number of patients*	*Disease*	*Time of follow-up*	*IBDQ score before/ after intervention*	*Intervention/ therapy*
Irvine *et al* 1995	305	CD	18 months	168/impairment in those requiring surgery	Cyclosporine
Casellas *et al* 2000	119	CD	median 34.5 months	No difference between groups	Comparison of HRQoL in medically and in surgically induced remission
Borgaonkar *et al* 2002	59	CD 36 UC 23	2 weeks	HRQoL impaired for the group receiving information	Impact of disease-related information on HRQoL
Feagan *et al* 2007a	728	UC	54 weeks	Significant improvement in all IBDQ subscores for the infliximab group	Infliximab/placebo
Langhorst *et al* 2007	60	UC	12 months	Mean per item 5.1/5.4 (intervention group), 5.2/5.4 (placebo), NS	Comprehensive lifestyle modification programme
Reinisch *et al* 2007	493 (206 in remission)	UC	30 weeks	130/195	Impact of remission induced by infliximab on HRQoL
Feagan *et al* 2007b	339	CD	60 weeks	Significant improvement in IBDQ subscores for the natalizumab group	Natalizumab/ placebo
Rutgeerts *et al* 2008	292	CD	12 weeks	132.2 (certolizumab pegol)/ 122.9 (placebo)	Certolizumab pegol/placebo
Loftus *et al* 2008	499	CD	56 weeks	Significant improvement in IBDQ subscores for the adalimumab group	Adalimumab maintenance therapy
Feagan *et al* 2009	425	CD	26 weeks	122.6/175.7 (certolizumab pegol), /167.9 (placebo)	Certolizumab pegol/ placebo
Dudley-Brown *et al* 2009	509	CD	12 weeks	123.6/150.3 (natalizumab) 122.5/137.7 (placebo)	Natalizumab/ placebo
Ng *et al* 2009	26	CD	12 months	137/176	TNFα-inhibitors in fistulizing CD
Bastida *et al* 2010	92	CD 68, UC 24	12 months	4.98/6.10 (mean score per item)	Thiopurines

CD = Crohn's disease; HRQoL = health-related quality of life; UC = ulcerative colitis

2.7.8 Worries and concerns of IBD patients

The most intense concerns of IBD patients in a US study were the uncertainty of the disease course, the effects of medication, the impact of the disease on energy level, the risk of having surgery or an ostomy bag, being a burden on others, loss of bowel control, and the risk of developing cancer. In CD, concerns about energy level, being a burden on others, not achieving full potential, having pain, and incurring financial costs were more pronounced than in UC, whereas concerns of developing cancer or other complications of the disease were more often seen in UC. Females were generally more concerned about issues associated with the body image, and younger individuals were more worried about impact of the disease on sexual intimacy (Drossman *et al* 1991). Females, patients with active disease, and overweight patients have higher levels of worries and concerns (Stjernman *et al* 2010).

The most intense concerns of patients with ileostomy were issues related to intimacy, access to medical care, energy level, loss of sexual drive, loss of ability to perform sexually, producing unpleasant odours, being a burden on others, attractiveness, and feelings about the body (Carlsson *et al* 2003).

2.7.9 Predictors of HRQoL in IBD

2.7.9.1 Disease-related factors

Disease severity and activity are the most important determinants of HRQoL as measured by the IBDQ (Irvine *et al* 1994, Casellas *et al* 2002, Hjortswang *et al* 2003) and the SF-36 (Hjortswang *et al* 2003). The need for hospitalization reflects the disease activity and is associated with lower HRQoL scores (Blondel-Kucharski *et al* 2001, Casellas *et al* 2002).

In most surveys, there were no significant differences in HRQoL between UC and CD patients after severity of disease had been taken into account (Casellas *et al* 2002, Guthrie *et al* 2002). A US study found that CD patients with colonic disease had better disease-specific (IBDQ) and generic (SF-36) HRQoL scores than had patients with small bowel disease or those with fistulizing or stricturing disease (Lix *et al* 2008). This finding was not seen in an earlier European study, in which disease activity determined the IBDQ scores, not the Vienna Classification (Casellas *et al* 2005b). The knowledge about impact of age on HRQoL is controversial, but longer disease duration may predict better HRQoL scores at least for some disease groups (Casellas *et al* 2002, Canavan *et al* 2006, Zahn *et al* 2006). Little is known about HRQoL in patients with both IBD and PSC. A recent study comprising 26 IBD-PSC patients and IBD patients without PSC, who were matched for gender, age, disease type and disease duration, found that both groups had similar SIBDQ scores (Ananthakrishnan *et al* 2010).

Patients who have undergone surgery for CD report worse HRQoL, as evaluated by IBDQ, than reported by non-surgical CD patients (Canavan *et al* 2006). After surgery for CD, HRQoL was improved 3 and 6 months postoperatively. After 12 months, due to

disease recurrencies, there was no significant difference for RFIPC score compared to preoperative values. However, for those patients still in remission, the postoperative HRQoL was significantly better than that preoperatively (Tillinger *et al* 1999).

The post-surgical situation of UC patients is different. After ileostomy and IPAA surgery, the function of the stoma or pouch is the most important determinant for HRQoL (McLeod *et al* 1986, Lepistö *et al* 2002). The impact of stoma on body image and self-esteem of adolescents is probably more pronounced (Nicholas *et al* 2008). In some studies, patients with stoma reported better quality of life than did those with an IPAA (Nordin *et al* 2002).

2.7.9.2 Patient-related factors

Psychiatric disorders (anxiety, depression, neuroticism and alexithymia) are important and independent predictors of poor quality of life in many surveys, and they affect the domain of social function most strongly (Guthrie *et al* 2002 Moreno-Jiménez *et al* 2007). Patients with psychological disorders also have significantly worse scores for domains that measure physical function, pain, and health perception in SF-36 (Guthrie *et al* 2002). In a study that controlled patients for disease activity, psychological factors were strongly associated with perceived health in IBD (Graff *et al* 2009). The negative impact of psychiatric disorders on perceived quality of life and symptom burden has been noted in other chronic diseases, as well (Katon and Ciechanowski 2002, Scott *et al* 2007).

Males are associated with better HRQoL scores in most surveys (Casellas *et al* 2002, Hjortswang *et al* 2003, Bernklev *et al* 2004), but not all (Han *et al* 2005). Concurrent smoking has a negative impact on HRQoL especially in CD (Blondel-Kucharski *et al* 2001, Casellas *et al* 2002, Bernklev *et al* 2004). However, a Canadian study found that smoking was related to a better quality of life for inactive IBD as measured by SIBDQ and EQ-5D (Farrokhyar *et al* 2006). A higher level of education was associated with better IBDQ scores in a Spanish study comprising 354 IBD patients, which probably was related to socioeconomical differences between the educational groups (Casellas *et al* 2002). In a Swedish study, the educational level did not affect generic or disease-specific HRQoL, nor did civil status, disease duration or disease extent (Hjortswang *et al* 2003). Even if disease duration does not have a significant impact on HRQoL, factors that affect HRQoL may change along with disease duration. In UC patients with disease duration of over 10 years, complications due to corticosteroids, such as osteoporosis, were thought to be the most striking factors that impaired HRQoL in a study performed in Japan (Kuriyama *et al* 2008). However, the medication of the study patients differed somewhat from preferred therapy in Finland.

A Canadian study found that patients with inactive IBD have significantly more functional gastrointestinal disorders than the general population as determined by Rome II criteria. These symptoms increase anxiety, and impair both generic (as measured by EQ-5D) and disease-specific (SIBDQ) HRQoL (Farrokhyar *et al* 2006). There is evidence that co-existing diseases impair HRQoL in IBD (Hjortswang *et al* 2003). Nevertheless, IBD

severity is the most important predictor of HRQoL for those with other chronic conditions in addition to IBD (Pizzi *et al* 2006).

Short-term benefits of some aspects of HRQoL and general well-being have been achieved with a comprehensive lifestyle modification programme which included stress reduction, stress management, and dietary and exercise guidance for 10 weeks. Three months after the intervention, patients of the intervention group showed significant improvement in the SF-36 scale compared with the usual-care control group. However, 12 months after the intervention, no difference was observed between the groups (Langhorst *et al* 2007). A group-based education programme for particularly anxious IBD patients did not improve their anxiety levels or HRQoL, although patients reported satisfaction with the programme and found information given on disease-related items useful (Larsson *et al* 2003). In another study, the provision of disease-related information in the form of educational booklets worsened short-term HRQoL as measured by IBDQ (Borgaonkar *et al* 2002). The same was seen in a Swedish study, in which a group-based intervention programme comprising educational lectures and therapy sessions was given. Those with short disease duration (≤3 years) benefited from the programme, whereas the HRQoL of patients with longer disease duration worsened during the follow-up (Oxelmark *et al* 2007).

2.7.10 Impact of individual IBD symptoms on HRQoL

During the development of the IBDQ, 77 ambulatory patients were asked about their problems related to IBD. The most disturbing symptoms were frequent or loose stools, abdominal pain and rectal bleeding. Patients experienced constitutional symptoms, such as fatigue, sleeping difficulties, and problems in maintaining weight as being more disturbing than emotional problems (irritability, anger and depression) or social problems (such as the need to cancel social events, or being unable to attend leisure-time activities, work or school). Even so, social and emotional problems were still seen as noteworthy. UC patients reported less fatigue and better well-being ($p<0.05$) than did the CD patients (Mitchell *et al* 1988). Non-inflammatory joint pain, which is common in IBD, significantly impairs IBDQ and SF-36 scores (Bernklev *et al* 2004, Palm *et al* 2005).

2.7.11 Impact of therapy on HRQoL

A Spanish survey reported that HRQoL (measured by IBDQ, EQ-5D, and PGWB) was similar for CD patients in remission, irrespective of whether remission had been achieved medically or surgically. The survey also included stoma patients (Casellas *et al* 2000). A large European survey found that two-thirds of patients (both UC and CD) rated their quality of life after surgery as greatly improved. However, after surgery, 65% of patients reported a recurrence of symptoms, and 58% reported postoperative complications (Ghosh and Mitchell 2007). In UC patients who had undergone colectomy and IPAA surgery, HRQoL highly depended on pouch function, and the patients with poor pouch function or

pouch failure had significantly lower SF-36 scores than did those with good pouch function (Lepistö *et al* 2002, Berndtsson *et al* 2007). In comparison, there were no significant differences in HRQoL scores (SF-36 and IBDQ) for UC patients with IPAA or permanent ileostomy after surgery, but those with restorative proctocolectomy appeared to have a better perception on body image (Camilleri-Brennan *et al* 2003).

HRQoL evaluations of most drugs used for IBD are available. Mesalazine has been shown to improve HRQoL significantly in mildly and moderately active UC (Irvine *et al* 2008). The use of immunomodulators is associated with a better HRQoL, whereas the use of corticosteroids has a negative impact on HRQoL of CD patients (Blondel-Kucharski *et al* 2001). Improved HRQoL, as measured by VAS and a questionnaire designed for evaluation of outcomes after surgery (Öresland *et al* 1989), was observed in patients with severe UC treated successfully with intravenous cyclosporine, compared to their peers who were treated surgically (Cohen *et al* 1999).

Infliximab has been shown to have a beneficial impact on HRQoL, as measured by IBDQ, and the increase is in parallel with improvements of CDAI (in CD) and Mayo (in UC) scores (Hanauer *et al* 2002, Reinisch *et al* 2007). With active or fistulizing CD, a rapid improvement in the IBDQ score was already evident after a single infusion of infliximab (van Balkom *et al* 2002).

2.7.12 Comparison of HRQoL with the general population and with other disease groups

Examined with a general HRQoL tool (SF-36) and a VAS, patients with colonic CD in remission did not differ from the general population. In contrast, patients with active disease scored lower for all the eight domains of SF-36, and those patients who had undergone surgery had lower scores for those domains that measured general health and physical role (Andersson *et al* 2003). A Swedish study found that inactive UC patients scored even better for the SF-36 dimensions of “physical function” and “bodily pain” than did the general population (Hjortswang *et al* 2003). UC patients with a well-functioning IPAA had similar SF-36 scores to those of the general population (Berndtsson *et al* 2007), although impaired scores for the domain that measures energy levels have also been reported (Lepistö *et al* 2002).

Psychological distress and impairment of HRQoL as measured by SF-36 were similar in irritable bowel syndrome (IBS) and IBD in a referral center setting (Pace *et al* 2003).

The 15D has earlier been used for IBD patients in a population-based survey that measured the impact of various chronic conditions on 15D and EQ-5D scores in a sample of citizens over 30 years of age. The respondents were matched for age, sex, income, education, marital status and other chronic conditions. The mean 15D score of IBD patients was 0.868, compared to the mean of all respondents of 0.910. Lower scores *inter alia* were determined for diabetes (0.833), urinary incontinence (0.835), rheumatoid arthritis (0.831), Parkinson’s disease (0.748) and macular degeneration (0.798). Patients with psoriasis (0.888), migraine (0.903), a loss of hearing (0.872) or disturbing allergy (0.894) had better scores than IBD patients (Saarni *et al* 2006).

3 Aims of the study

The aims of the present study were to find answers to the following questions:

1. Do Finnish IBD patients have symptoms as frequently as other European patients, and are the arrangements of their therapy different from those of other patients in Europe? (Study I)
2. Which demographic and therapy-associated factors influence HRQoL as measured by the disease-specific IBDQ instrument? (Study II)
3. Is the generic 15D instrument useful for the evaluation of HRQoL in IBD, and do IBD patients have lower 15D scores than those of the general population sample? (Study III)
4. Do IBD patients have more comorbidities than those of the general population, and do comorbidities impair HRQoL? (Study IV)

4 Patients and methods

4.1 Patients and data collection

The study was performed in cooperation with a patient organization, the Crohn's and Colitis Association of Finland. Most of the study patients were recruited from the patient organization member register, but an additional sample of individuals who had received special reimbursement for IBD medication, as recorded in the register of Social Insurance Institution of Finland, was recruited. The study was performed as a postal survey, by which the study questionnaire was first mailed to 3852 adult (over 18 years of age) members of the patient organization in September 2006. The study questionnaire was posted to an additional 1490 adult patients selected by random sampling from the national register in February 2008. The national register included about 30 000 individuals who were eligible for reimbursement for IBD medication. The two study populations included an overlap of the same individuals (total of 82 respondents), and for those, the latter response was included in the analysis. No reminders were sent.

4.2 Questionnaires

The study questionnaire comprised the 32-item, disease-specific IBDQ and the 15-item, generic 15D questionnaires. These were complemented by the European Federation of Crohn's and Colitis Associations' (EFCCA) questionnaire with 31 questions about the following: the diagnosis and history of the disease, current and previous therapies, IBD symptoms and their frequency, and the impact of the given therapy and symptoms on the experienced HRQoL. The study questionnaire also included a section that inquired about the utilization of health care services (not in the scope of this thesis). The IBDQ was used under licence from McMaster University, Hamilton, Canada, and the EFCCA gave permission to use their questionnaire. Small modifications were made to the EFCCA questionnaire (such as including additional questions about the education level of the respondents).

The IBDQ and EFCCA questionnaires were translated into Finnish and Swedish by official translators of the Helsinki University Language Services. A back-translation to English was performed to confirm the linguistic accuracy of the translation. The 15D was originally available both in Finnish and in Swedish. The questionnaire was then tested on a group of 60 IBD patients who were members of the Crohn and Colitis Association and all the questions were easily understood.

Some patients did not answer all the questions in the questionnaire. In such cases, the mean scores of IBDQ were calculated from the other items of the domain. If two or more questions per domain were unanswered, or if the total number of unanswered items

exceeded four, the patient was omitted from analyses, as the results and scores would not have been reliable. If the subject had left one to three questions of the 15D unanswered, the missing data were replaced by predictions from linear regression analysis, based on the other dimensions and using age and gender as the independent variables (www.15d-instrument.net). For the EFCCA questionnaire, percentages were calculated of those patients who had given an answer to the relevant question.

The Finnish versions of the 15D and EFCCA questionnaires are presented in Appendix A. Per the terms of the license agreement, the IBDQ questionnaire can not be published.

4.3 Control groups

In study I, the differences in the diagnosis of IBD, current and previous therapies, frequency of IBD symptoms, the impact of symptoms and given therapies between the Finnish and the European patients were compared. The European control group comprised the 5576 IBD patients who had participated in a survey conducted by EFCCA with seven of its national organizations. The participating countries were Denmark, Italy, The Netherlands, Portugal, Spain, Switzerland, and the United Kingdom (Ghosh and Mitchell 2007).

The examination of the generic 15D scores of IBD patients in study III used a general population sample obtained from the national Health 2000 Survey (for subjects ≥30 years of age) (Aromaa *et al* 2004) and from the Finnish National Health Survey 1995/96 (for subjects 18-29 years of age). These population samples were matched for age and sex, and served as a control group.

In study IV, two control subjects for each participant that were matched for age, gender and hospital district were chosen from the Social Insurance Institution register. The aim of study IV was to compare patients with IBD with the general population, and the reference group included patients with IBD in proportion to their prevalence in that particular population (0.7%). No HRQoL data were available for the control group.

4.4 Statistical methods

Statistical analyses were performed using SPSS for Windows versions 14.0-16.0 statistical software (SPSS Inc, Chicago, Ill., USA). In study I, Confidence Interval Analysis version 2.1.2 (CIA, Statistics with confidence; BMJ Publishing Group Ltd., London, UK) software was utilized.

The results are presented as percentages, means with standard deviations (SD), or medians. In study I, 95% confidence intervals (CI) were used. The percentages are reported as integral numbers when they exceed 10, and to one decimal place for percentages less than 10. In studies I and IV, comparisons of continuous variables

between the groups were performed by using analysis of variance (ANOVA). Moreover, ANOVA was used in study II to examine how differences in the frequency of symptoms, the level of satisfaction with current treatment, and the arrangement of therapy affected the IBDQ scores. In studies II and III, linear regression analysis served to estimate how individual demographic factors, symptoms and medications affected HRQoL scores. Linear regression was also used for studying the patient characteristics and risk factors for CHD in study IV.

In study III, the 15D scores were not normally distributed, thus differences in continuous variables were analysed by the Kruskal-Wallis test when more than two groups were present, or by the Mann Whitney U–test to examine differences between two groups. Furthermore, in study III, correlations between 15D and IBDQ scores were tested by using Pearson's correlation coefficient whereas differences in the 15D scores between study patients and the reference population were analysed by the independent samples *t*-test.

In study IV, the Cox regression model was used for examining the differences in the occurrences of chronic diseases between IBD patients and their controls. The analysis was performed using a conditional logistic regression model that was technically implemented by using the Cox regression model. The matched case-control group variable was handled as a stratum, and the follow-up time within each matched case-control subject was set to 1 so that that the cases and controls were at risk at the same time. Further, partial correlation with matching for age was used for estimating the impact of various chronic diseases on HRQoL scores. For categorical variables, tests were performed with the chi-square test in all studies.

Many patients reported taking several different medications. Therefore, dummy variables were used for investigating the impact of separate therapies on IBDQ scores in study II. The dummy variables comprised subjects with no medical treatment, subjects with only 5-ASA medication, subjects with immunosuppressive therapy but no biological medication or corticosteroids, subjects with biological treatment but no corticosteroids and subjects who were having corticosteroid treatment (with any other treatment) at the time of the survey. In study II, the impacts of each demographic factor and given therapy on the IBDQ score were examined by using a sequential ANOVA approach, in which the symptoms were first accounted for in the model. Thereafter, the effect of each factor in turn was evaluated based on its respective residual variability in the IBDQ score.

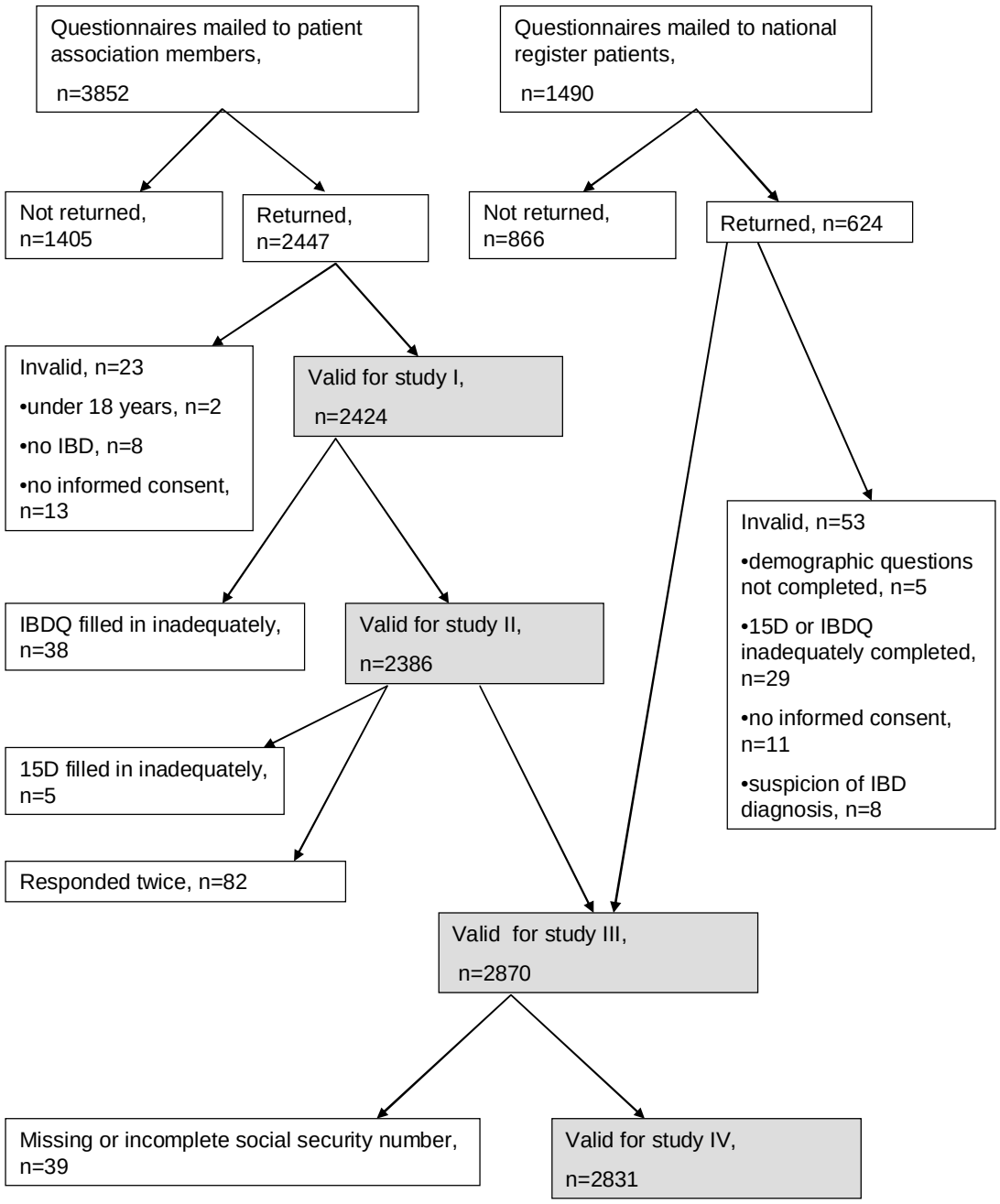
The study population was divided into four subgroups according to the following diagnoses: UC, CD, proctitis and indeterminate or unspecified colitis (IC). As the last two subgroups were considerably smaller than the first two, statistics were in some cases calculated only for the UC and CD groups. In study IV, statistical analyses were performed only for UC and CD groups, and patients with proctitis were included in the UC group.

A p-value of less than 0.05 was considered statistically significant.

4.5 Ethical considerations

The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District (registration number 94/E5/06). All participants gave their written informed consent for the HRQoL study and for the access and acquisition of their data from the Social Insurance Institution register. Non-respondents and control patients selected from earlier population-based HRQoL studies or from the Social Insurance Institution register could not be identified.

Figure 2. Flow chart of the patients in studies I-IV



5 Results

5.1 Recruited patients (I, II, III, IV)

Of the total of 5342 questionnaires mailed, 3071 (57%) were returned. Of those questionnaires sent to patient association members, 64% were returned, whereas the percentage was 42% for those mailed to patients who were selected from the Social Insurance Institution register. Of all the respondents, two were under 18 years, 16 reported or were suspected of not having IBD, and 24 had not signed the informed consent. An additional 116 subjects had omitted their social identity numbers, which made their reimbursement data unobtainable from the Social Insurance Institution, or had failed to complete either of the HRQoL questionnaires adequately for the accurate calculation of the HRQoL scores. A total of 82 patients had responded twice. For each study, all the suitable patients were included. Figure 2 shows the flow chart of the study population.

5.2 Demographic characteristics of the patients and comparison with the European study (I, III)

The results are given for the patient association cohort, as the control population in the European EFCCA study also comprised members of IBD patient associations. Differences between patient association members and patients recruited from the Social Insurance Institution register are given in Table 5.

Of the respondents with valid responses, the majority were female. The gender difference was mostly due to the female predominance among the members of Crohn and Colitis Association, for which about two-thirds are female. A predominance of females, (57%) was also observed in the European EFCCA study (Ghosh and Mitchell 2008). In the current study, the majority (53%) were diagnosed with UC, 37% with CD and the rest with proctitis or unspecified colitis. The distribution of diseases was somewhat different in the European study with 57% of patients having CD. In the European study, patients were divided into groups of CD and UC, and the smaller group of those having IC was excluded from the analyses. Demographic characteristics of the study population are shown in Table 5.

Table 5. Demographic characteristics of patients and differences between samples (studies I & III)

	Patient association sample			**Social Insurance Institution sample**		
Characteristics	*All (n=2424)*	*CD (n=961)*	*UC (n=1257)*	*All (n=594)*	*CD (n=154)*	*UC (n=337)*
Age (years)						
Mean	43.3*	43.7*	43.0*	49.8*	47.9*	49.6*
Median	42.2	41.9	41.6	48.8	46.9	48.7
Range	18-85	18-85	18-82	18-89	23-89	20-89
Gender						
Female	67.0%*	67.1%*	65.4%*	51.5%*	60.4%*	52.8%*
Male	33.0%	32.9%	34.6%	48.5%	39.6%	47.2%
Duration of IBD (years)						
Mean	9.5*	10.2*	9.5*	12.9*	11.9*	13.9*
Median	8.0	8.0	7.0	10.0	11.0	10.0
Range	0-50	0-40	0-50	0-50	0-40	0-50
Marital status						
Single	16.7%	17.8%	16.4%	14.0%	16.2%	12.8%
Married/ common-law	73.5%	72.1%	74.6%	72.5%	68.8%	75.0%
Widowed	2.3%	2.5%	2.0%	3.5%	1.9%	3.6%
Divorced	7.5%*	7.5%*	6.9%	9.9%*	13.0%*	8.6%
Education level						
Comprehensive school	13.4%*	15.3%	11.9%	20.0%*	20.3%	16.7%
Vocational school	21.5%*	22.9%	21.3%*	26.6%*	29.4%	27.2%*
High school	10.2%	10.2%	10.6%*	7.6%	11.8%	6.3%*
College/institute	40.7%*	39.3%*	41.3%*	31.5%*	28.2%*	33.8%*
University	14.1%	12.2%	15.0%	14.2%	10.5%	16.1%
Symptoms prior to meeting specialist (years)						
Mean	2.9	4.0	2.2	2.8	3.7	2.4
Median	1.0	2.0	0.6	1.0	2.0	1.0
Range	0-50	0-50	0-50	0-40	0-40	0-30
Family history of IBD						
Yes	13.5%*	13.6%*	12.7%*	19.5%*	15.8%*	21.3%*
No/no answer	86.5%	86.4%	87.3%	80.5%	84.2%	78.7%

CD = Crohn's disease; UC = ulcerative colitis; IBD = inflammatory bowel disease

**indicates significant difference between the patient association and the Social Insurance Institution samples*

The females were younger than the males (43 years vs. 45 years, $p<0.001$). The mean duration of the disease was 9.6 years (SD 7.8) and 277 (11%) had been diagnosed with IBD at least 20 years earlier. In those patients, rates of CD and UC were close to each other (48% versus 50%). The mean duration of the disease was shorter than that found in the European study, for which almost three-quarters of the patients had been diagnosed more than five years earlier. This contrasts with the current study in which only 61% had had the disease for over five years. The study population included 190 patients who had been diagnosed within a year and a majority (54%) of them had UC. At least one first-grade relative (parent, sibling or child) diagnosed with IBD was reported by 16% of CD patients and by 14% of UC patients, which was slightly more than that observed in the European survey (12% for the whole study population). UC patients had received tertiary education significantly more often than the CD patients ($p=0.014$). The reason for the educational difference remains unexplained, and the level of education was not explained by current activity of the disease or by the history of surgery.

The European study inquired as to whether the patients had been diagnosed by a family physician, gastroenterologist, or other type of physician. Due to the different arrangement of the health care system in Finland, in the current study the patients were asked whether they had been diagnosed by a health center physician or occupational physician, specialist (gastroenterologist, surgeon, or specialist in internal medicine), or by any other type of physician. A marked difference emerged in the way that diagnosis of IBD was made in Finland and elsewhere in Europe. In the European study three-quarters of respondents were diagnosed by a gastroenterologist, whereas the percentage in the current Finnish study for those diagnosed exclusively by a specialist was 96%. No difference in the rates could be seen for those patients diagnosed more than 20 years ago and for those diagnosed more recently. Moreover, 81% of the patients reported being currently followed-up only by a gastroenterologist and for the remaining 19%, an occupational or general physician took part in the therapy. In Europe, a quarter of patients reported at least some involvement of their family physician.

Both in the current study and in the previous European study patients reported long delays before seeing a gastroenterologist after the emergence of the first IBD symptoms. In our study, over 50% stated that they had experienced symptoms for a year or longer before meeting a specialist, and 13% had waited for over five years. For the CD group the delay was particularly long, a mean 4.0 years (median 2.0 years) and 19% reported delay of over five years.

5.2.1 Rates of surgery (I)

The rate of patients who had undergone surgery was high, 43%, for CD, and five patients had undergone 10 or more operations due to their illness. The percentage of surgery for UC was considerably lower, 12%. Rates of surgery were even higher in the European survey for both CD (58%) and UC (14%). Over a quarter of operated patients reported serious postoperative complications in both surveys. Furthermore, 4.6% of CD patients and 1.4% of UC patients had a stoma after surgery and 8.5% of UC patients had an IPAA.

The rates of surgery are shown in Table 6. Although postoperative recurrence of symptoms was reported by 67% of CD and 34% of UC patients, over 90% of CD patients and 85% of UC patients stated that their quality of life had improved in the months following surgery. Similar rates could also be seen in the European study.

Those CD patients who had undergone surgery, experienced more disturbing symptoms than did those treated conservatively. After surgery, 22% of CD patients had symptoms that greatly interfered with their leisure activities (13% in the non-surgery group, $p<0.001$) and 19% had symptoms that greatly affected their ability to work (11% in the non-surgery group, $p<0.001$). In addition, UC patients with either stoma or IPAA felt more disabled than did the patients who had not undergone surgery.

Table 6. Rates of surgery (study I)

	Crohn's disease (n=961)	*Ulcerative colitis (n=1257)*	*Proctitis (n=121)*	*Indeterminate or unspecified colitis (n=85)*
Operations for IBD				
Yes	42.6%	12.3%	2.5%	6.0%
No/no answer	57.4%	87.7%	97.5%	94.0%
Postoperative situation				
Stoma	4.6%	1.4%	0.0%	0.0%
IPAA	0.4%	8.5%	0.0%	1.2%

IBD=inflammatory bowel disease; IPAA= ileal pouch-anal anastomosis

5.2.2 Symptoms and extraintestinal manifestations (I)

The most common IBD symptoms reported were painful abdominal cramps, persistent or recurrent diarrhoea, rectal bleeding, and fatigue. Over half of the CD patients had suffered from joint pain associated with their disease. The percentage for UC was also high, 47%. In the small group of patients with proctitis, fewer than 30% reported a history of joint pain.

Comorbidity with ankylosing spondylitis was reported by 3.3% of patients, with the highest percentage being in the CD group, 5.3%. The results were similar for the European study.

5.2.3 Frequency and impact of symptoms on daily life (I, II and III)

Impact of the disease on daily life was notable: 37% reported suffering from disturbing symptoms weekly, as the percentage was 10% in the European study. The symptoms

greatly affected the ability to enjoy leisure activities in 17% of the patients, and in 14% of the patients they greatly affected the person's capacity to work. In addition, many patients reported inconvenience during leisure activities (51%) or at work (45%). In the European survey, the rate of patients who experienced difficulties at work or during the pursuit of leisure activities was somewhat higher. No significant gender or age difference was seen for disease activity. Patients recruited from the patient organization and from the national register had no differences in disease activity as measured by the frequency of symptoms. CD patients with a history of surgery reported a more active disease than did those who had not undergone surgery (p=0.025) with 45% suffering from weekly IBD symptoms. Table 7 shows the rates of symptoms associated with IBD.

Table 7. Symptoms of inflammatory bowel disease (study I)

Symptom	*Crohn's disease (n=961)*	*Ulcerative colitis (n=1257)*	*Proctitis (n=121)*	*Indeterminate or unspecified colitis (n=85)*
Painful abdominal cramps	71.3%	64.3%	52.9%	70.6%
Persistent or recurrent diarrhoea	76.5%	81.5%	60.3%	75.3%
Loss of appetite	39.8%	31.0%	17.4%	34.1%
Rectal bleeding	54.6%	83.4%	82.6%	71.8%
Weight loss	48.5%	44.7%	26.4%	43.5%
Fever	43.0%	30.9%	10.7%	32.9%
Joint pain	53.9%	46.5%	29.8%	54.1 %
Fatigue	54.7%	51.8%	30.6%	45.9%
Skin tags	22.4%	12.8%	14.9%	12.9%
Fistulas	19.9%	3.3%	2.5%	5.9%
Sores around the anal area	32.2%	26.2%	33.9%	28.2%

Adapted from: Haapamäki *et al* 2008

5.2.4 Current therapy (I, III)

Only 4.2% of the patients reported not taking any IBD medications at the time of the survey, compared with as many as 18% in the European study. Two-thirds reported a previous intake of corticosteroids and over one-fifth were taking corticosteroids at the time of the survey. The current use of immunomodulators was reported by 33% of all patients, as the rate for CD was significantly higher 44% (p<0.001). The numbers are higher than in the European survey, which found that 31% of CD patients and 19% of UC patients were receiving immunomodulators. At the time of the first mailing of the questionnaires (in 2006), infliximab was the only biological medical treatment indicated for IBD. A few patients reported that they were receiving adalimumab off-label. Current or previous use

of biologicals was reported by 193 patients (8.0%) in the patient association sample, and over 80% of them had CD. The percentage was lower, 3.9%, for the national register sample, mainly due to different disease distribution (CD 26%, UC 59%).

5.2.5 Patient satisfaction (I)

Despite the burden of symptoms on daily life, the great majority (93%) of patients expressed satisfaction with their current treatment and only 1.4% were very dissatisfied. Dissatisfaction was at least partly related to treatment resistant disease activity, as 60% of the very dissatisfied subjects had weekly symptoms of IBD. When asked about the impact of different therapies (steroids, immunomodulators, biologicals and surgery) on the quality of life, all therapies were associated with at least some level of increased quality of life during the months following treatment for over 70% of the patients. Those consulting a specialist during follow-up, expressed satisfaction more often with their current therapy than those being followed-up by general practitioners or occupational doctors (94% versus 89%, p=0.02).

The level of satisfaction was higher in the current study than that found in the previous European EFCCA study, in which only 76% expressed satisfaction with their current treatment.

The majority of the patients (60%) stated that their doctors had never asked about the impact of their IBD symptoms on their quality of life.

5.3 Comorbidity (IV)

Reimbursements for chronic diseases in addition to IBD were observed in 29% of the patients. On the other hand, 0.7% of the control subjects, who were matched for age, gender and hospital district, had reimbursement for IBD, a percentage that was proportional to the actual prevalence of IBD in the population (Statistical Yearbook of the Social Insurance Institution 2008).

Significant increases in frequencies of connective tissue diseases ($p<0.001$), asthma and chronic obstructive pulmonary diseases ($p<0.001$), pernicious anaemia ($p<0.001$) and coronary heart disease ($p=0.004$) were associated with IBD. No differences in the occurrence of malignant diseases were seen. Malignancies were relatively rare for both IBD patients and for the controls, with a prevalence of less than 1%. The most prevalent comorbid diseases are presented in Table 8.

Females with IBD in particular appeared to be at increased risk of CHD (1.6-fold, $p=0.014$) compared with their peers in the general population. The comparable CHD risk of the male IBD patients was only just significantly increased ($p=0.046$), but it was still over two-fold compared to the female IBD patients (1.4% versus 3.4%, $p=0.043$ after controlling for age). For those patients diagnosed with IBD at over 50 years of age ($n=299$, current mean age 64 years), the CHD prevalence was only just significantly

higher than for their peers in the general population (9.7% versus 6.0%, p=0.045). Patients with both IBD and CHD were slightly, but non-significantly, younger than patients with only CHD (64.5 versus 66.2 years). IBD had been diagnosed earlier than CHD in 66% of the cases.

Those with the most active disease (weekly symptoms) had a higher risk of having other chronic diseases in addition to IBD, than did those patients with less active disease (p=0.028 between the groups). IBD activity was especially related to prevalence of CHD (p=0.030), chronic cardiac insufficiency (p=0.030), pernicious anaemia (p=0.022), epilepsy (p=0.010), and glaucoma (p=0.007).

Table 8. The most important diseases conferring entitlement to a special refund under national health insurance

	Frequency in controls (n=5662)	*Frequency in IBD patients (n=2831)*	*Frequency in CD (n=1054)*	*Frequency in UC (including proctitis) (n=1661)*
Chronic cardiac insufficiency	0.3%	0.5%	0.4%	0.7%
Connective tissue diseases, rheumatoid arthritis	2.0%*	3.9%*	5.4%†	3.0%†
Chronic asthma and obstructive pulmonary diseases	4.3%*	7.1%*	7.0%	7.3%
Chronic hypertension	7.5%	8.1%	8.3%	7.7%
Chronic coronary heart disease	1.4%*	2.2%*	2.2%	2.0%
Chronic arrhythmias	0.6%	0.6%	0.6%	0.5%
Diabetes mellitus	2.6%	2.3%	1.7%	2.3%
Thyroid insufficiency	1.7%	1.9%	1.6%	2.0%
Pernicious anemia	0.2%*	4.1%*	10.3%†	0.3%†
Multiple sclerosis	0.2%	0.1%	0.0%	0.1%
Epilepsy and comparable convulsive disorders	1.4%	1.1%	0.9%	1.1%
Severe psychotic and other severe mental disorders	2.3%*	1.6%*	1.7%	1.4%
Glaucoma	0.7%	0.9%	0.9%	0.9%
Cancer or leukemia	0.9%	0.8%	0.9%	0.6%

**,† significant difference between groups (controls/IBD patients, or CD/UC); IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis*

5.4 IBDQ scores (II, III, IV)

Of all the patients, 63 had filled in the IBDQ inadequately for calculating the scores, and a further 171 patients had left single IBDQ questions unanswered. The total IBDQ scores ranged from 43 to 224 in the current study, as the possible range is 32-224. The mean total score was 163 (SD 35.1). As in many earlier studies, females had significantly lower scores (161, SD 34.8) than did males (168, SD 35.5) ($p<0.001$), and males had higher scores for all dimensions except for social functions. However, the medians of the total scores were closer to each other, 166 in females and 168 in males. The sample taken from the patient association scored significantly worse (mean 163) than that of the national register (mean 170) ($p<0.001$).

Those who had been diagnosed within the last five years, scored significantly lower than those with a longer-lasting disease, and particularly low scores were seen in those who had been diagnosed during the previous year (154, SD 34.8, $p<0.001$). Older age also affected the scores, and patients over 50 years of age had significantly lower scores than did younger patients, 159 (SD 35.4) versus 165 (SD 34.9) ($p<0.001$).

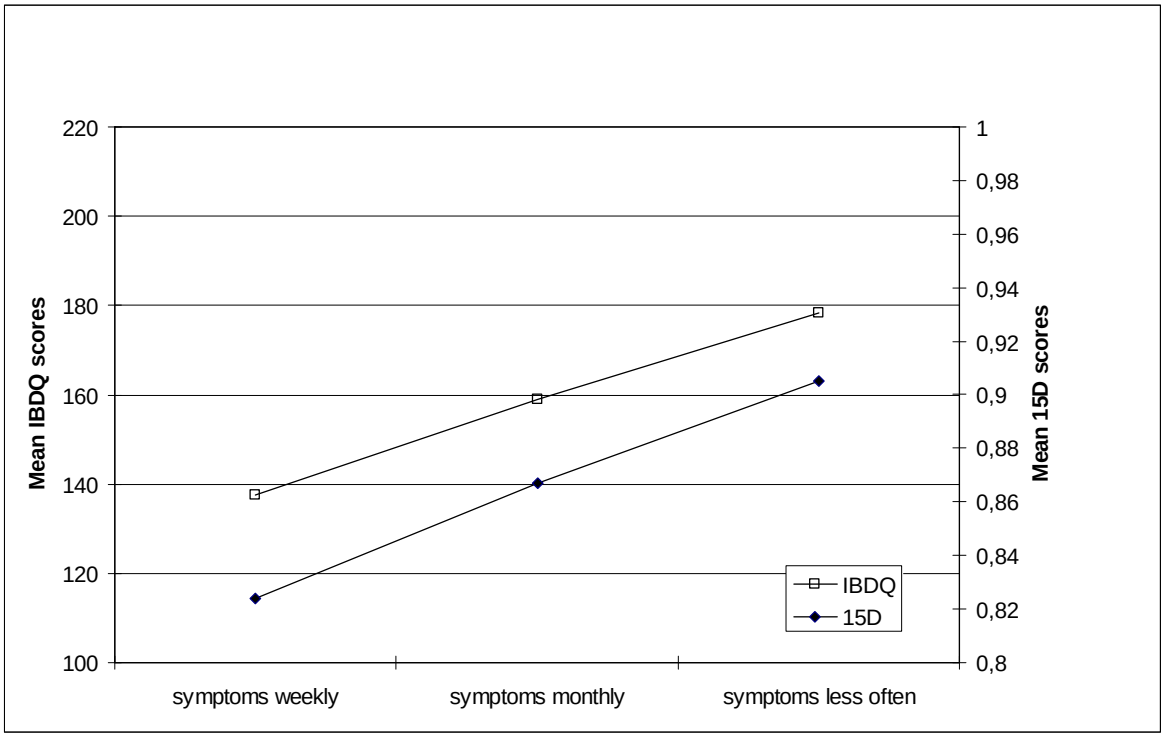
There was a statistically significant difference in the scores between UC and CD, but the difference disappeared, when the groups were adjusted for disease activity.

Disease activity had a great impact on the IBDQ scores as shown in Figure 3. The mean score was 136 (SD 32.1) for patients with weekly symptoms, compared to 177 (SD 26.8) for those who suffered from IBD symptoms only occasionally ($p<0.001$). Satisfaction with current treatment also reflected the scores, and for those who expressed satisfaction, the mean score was 166 (SD 33.4) compared to 124 (SD 34.7) for dissatisfied subjects ($p<0.001$). No significant differences existed between patients who were being followed-up by specialists and those who were being followed-up by occupational doctors or general practitioners.

The history of surgery impaired IBDQ scores in this survey, and a mean IBDQ score was 158 (37.2) for those who had undergone surgery compared to 166 (SD 33.7) for non-surgical patients ($p<0.001$). No significant post-surgical difference between UC and CD was detected. In general, the patients with IPAA (156, SD 40.8) or stoma (153, SD 36.1) had even lower scores compared to all surgical patients.

Comorbidity with other chronic reimbursed diseases was also associated with significantly impaired IBDQ scores. As IBD patients without other chronic diseases had a mean IBDQ score of 168 (SD 34.3), those who had any other reimbursed disease scored 157 (SD 36.2) ($p<0.001$). Patients with hypertension, pernicious anaemia and severe mental disorders in particular had lower scores than average ($p<0.001$).

Figure 3. Mean 15D and Inflammatory Bowel Disease Questionnaire (IBDQ) scores and frequency of inflammatory bowel disease symptoms



Possible range is 0 to1 for the 15D and 32 to 224 for the IBDQ. A higher score indicates better quality of life.

Figure adapted from: Haapamäki *et al* 2010

5.5 15D scores (III, IV)

More than three 15D questions were unanswered by five respondents who were therefore omitted from the analyses. Single questions were left unanswered by some respondents, and the total number of unanswered questions was 188. The question that considered sexual activity had been left unanswered by 64 respondents. The range of 15D scores was 0.30-1.00, with a mean of 0.87 (SD 0.097). A ceiling effect was observed as 6.2% of patients scored 1.00 (perfect health). Disease activity was strongly associated with the score even after differences in scores were adjusted for age, gender and diagnosis ($p<0.001$). Figure 4 shows the 15D profiles in groups of different disease activity. Gender or disease type had no significant impact on the scores but older age was related to lower scores. Both groups of newly-diagnosed patients and patients with a long-lasting disease had lower scores even after adjusting for age. After surgery, the mean score was

Figure 4. 15D profiles by frequency of inflammatory bowel disease symptoms.

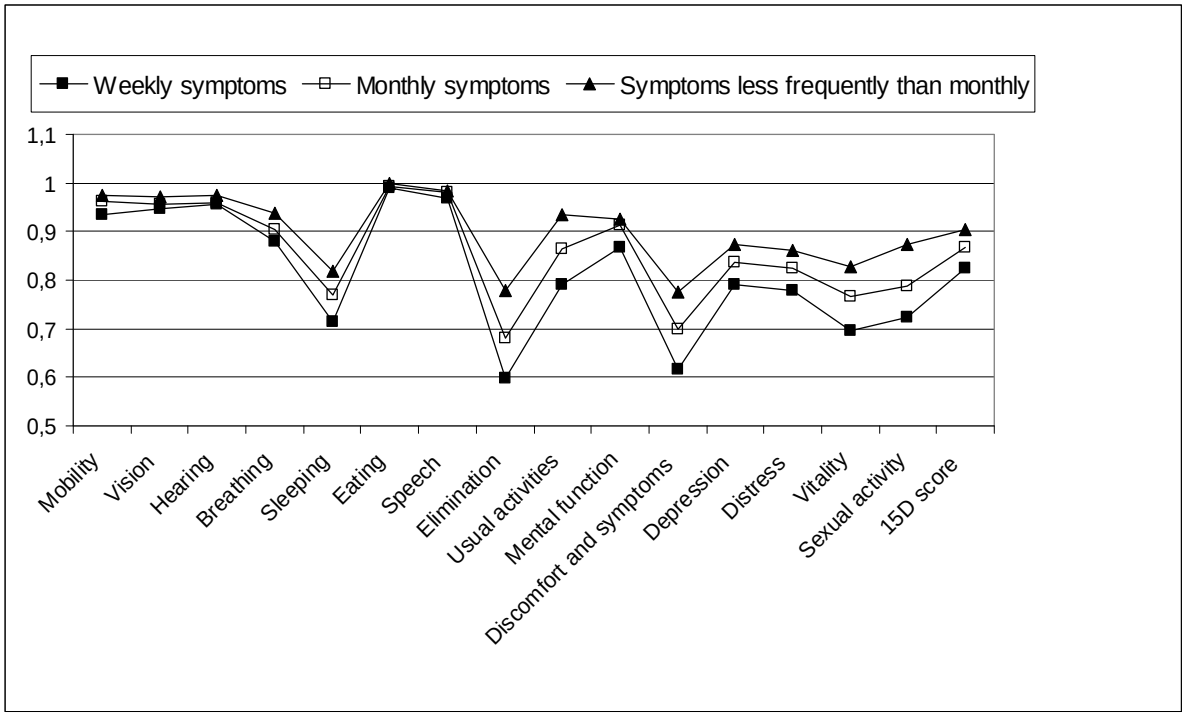


Figure adapted from: Haapamäki *et al* 2010

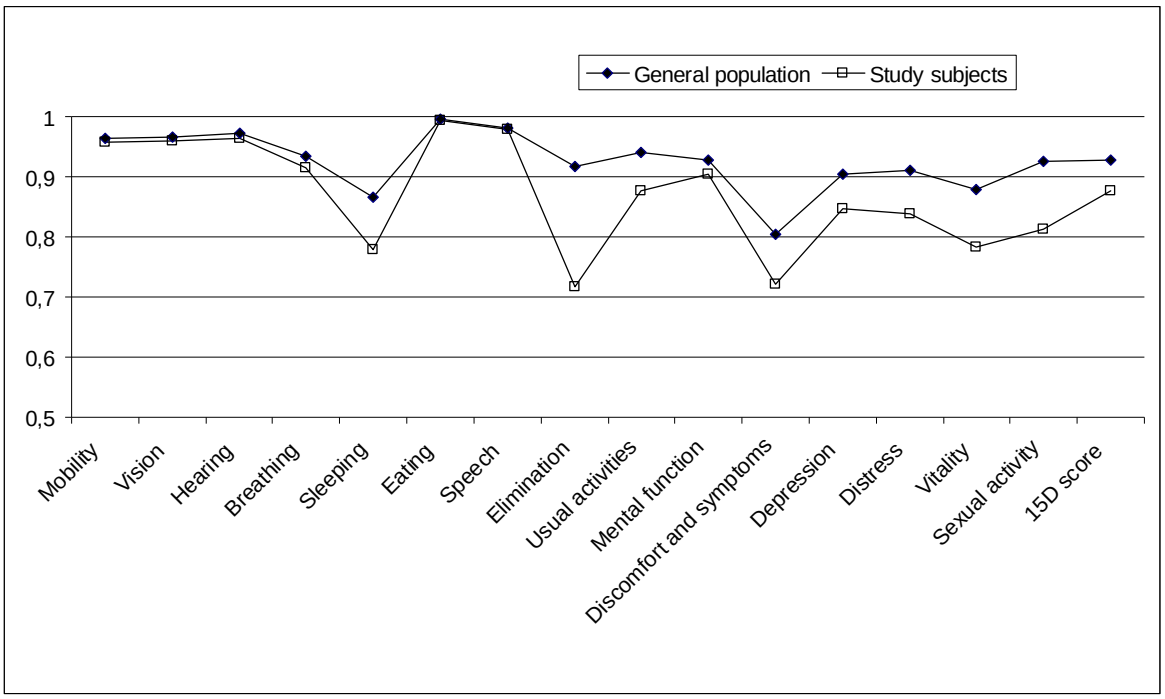
significantly lower than in patients who had not had surgery, 0.85 versus 0.88 ($p<0.001$) and it was 0.84 for stoma patients. No significant differences emerged between patients who were being followed-up by specialists and patients who were being followed-up by occupational doctors or general practitioners. Again, patient association subjects had significantly lower scores than other patients (0.87 versus 0.88) ($p=0.002$).

As observed with IBDQ, comorbidity with other chronic conditions was associated with impaired 15D scores. Suffering from any other chronic reimbursed disease impaired significantly the 15D score ($p<0.001$). Most strikingly this was seen for hypertension, obstructive pulmonary diseases and severe mental disorders ($p<0.001$).

The 15D score appeared to be strongly related to the total IBDQ score (Pearson's correlation coefficient of 0.733, $p<0.001$), which indicates its applicability for the measurement of HRQoL in IBD patients (Figure 3).

The age and gender-standardized population sample had significantly higher scores for all dimensions, except for speech (Figure 5). Not even the IBD patients who reported symptoms less often than monthly could achieve the 15D level of the controls (mean scores 0.902 for IBD versus 0.927 for controls). Differences in 15D scores in addition to other results between the two samples are shown in Table 9.

Figure 5. 15D profiles of the study group and of an age- and sex-standardized sample from the general population



All differences are significant except for speech (mobility, p=0.023; vision, p=0.003; eating, p=0.032; for other dimensions, p<0.001).
Figure adapted from: Haapamäki *et al* 2010

Table 9. Comparison of results of the patient association and of the Social Insurance Institution samples (III, IV)

	Patient association sample	*Social Insurance Institution sample*	*p*
Active disease (weekly symptoms)	37%	36%	NS
Satisfaction with current therapy	93%	92%	NS
Rate of surgery	25%	16%	<0.001
IBDQ score	163	170	<0.001
15D score	0.87	0.88	0.002
Frequency of connective tissue diseases	4.2%	2.7%	0.014*
Frequency of CHD	1.9%	3.4%	NS*
Frequency of asthma or chronic obstructive pulmonary disease	6.9%	8.0%	NS*

*IBDQ = Inflammatory Bowel Disease Questionnaire; CHD = coronary heart disease; NS = not significant; *= analyzed after controlling the groups for age*

6 Discussion

6.1 Patients and methods

At the end of year 2007, the Social Insurance Institution register comprised 30 051 patients (both children and adults) who were eligible for reimbursement for IBD medication (Statistical Yearbook of the Social Insurance Institution 2008). Therefore, the study subjects represented over 9% of Finland's IBD population. The questionnaires were mailed only once, and no reminders were subsequently sent. Nevertheless, the response rate was still 57% (63% for members of Crohn and Colitis Association), which can be considered as satisfactory.

The Social Insurance Institution register comprises mainly patients with current or earlier IBD medication, and for example UC patients who end up to colectomy very soon after the diagnosis may not have claimed for reimbursement for their IBD medication. Nonetheless, the reimbursement register can be considered as very representative of the whole IBD population.

Most of the surveyed patients were members of the patient association. The possible differences between members and non-members are not fully known, but being a member may indicate that the subject has found his/her disease problematic in some way. The patient association members had significantly lower HRQoL scores than those of the patients who were recruited from the national register, although no differences in disease activity were detected between them and the patients recruited from the national register. It should be noted, however, that the rating of disease activity was based solely on the subjective information obtained from the respondents, not on clinical or endoscopic scores. Consequently, the 'activity of the disease' as experienced by the respondent does not necessarily equal that of the true activity of the disease. Moreover, the division of activity into three levels according to frequency of symptoms is robust. Nevertheless, getting more specific data would have been difficult with self-administered questionnaires.

Due to confidentiality regulations, no information about the non-respondents was available. Returning of the questionnaires was optional, and it is possible that those who returned the questionnaire may have felt more disabled due to their disease, or may have been more aware of issues concerning HRQoL. Some respondents did not answer all the questions in the questionnaire. At less than 1%, the number of unanswered questions was relatively small, however.

No significant difference in the prevalence of IBD between genders has been evident in epidemiological surveys (Loftus 2004, Vind *et al* 2006), but due to the gender distribution of the patient association, our sample had a predominance of females. In the sample obtained from the national register, 52% of the respondents were female, which indicates no significant differences in response rates between the sexes. The study population included patients of different age groups and from different parts of the country, who lived in either a city and or in rural areas, thus the samples can be considered representative of the IBD population in Finland.

The postal survey design of the survey had its advantages and disadvantages. We reached patients from all over the country by mailing the questionnaires, and the patients were followed-up in various hospitals instead of a single or a few centers. On the other hand, the only information about the diagnoses, symptoms and therapies came from the patients themselves. The Social Insurance Institution register included systematic data on exact diagnoses for those diagnosed in 2000 and later. However, most patients appeared to be well aware of their diagnosis and a few patients who were unsure of the diagnosis were classified into the group of unspecified colitis, which was mostly not used for statistical calculations because of its small size.

The study population included 58 subjects with a stoma. In all respects, the IBDQ questionnaire is not ideal for them, as it includes questions about frequency of bowel movements and continence. Nevertheless, the views of stoma patients were still of importance, so they were included in the analyses. The IBDQ has also been used in stoma patients in other surveys (Nordin *et al* 2002, Camilleri-Brennan *et al* 2003, Watanabe *et al* 2006).

6.2 Symptoms and therapy (I, II, III)

The time from first IBD symptoms to diagnosis was strikingly long in our study, as over half of the respondents reported symptoms for a year or longer before having an examination by a specialist. The delay was especially long for CD patients, and exceeded the time intervals reported in earlier studies (Vind *et al* 2006). As there were a few very long reported delays, the median is probably a more informative parameter of the actual situation. It is noteworthy, that the time before diagnosis was not significantly shorter for the patients diagnosed during the past 10 years. This finding suggests that despite the new diagnostic tools and an increased number of gastroenterologists, a suspicion of CD does not always arise because of the sometimes obscure or indefinite symptoms. Many of the patients who reported long delays before meeting a gastroenterologist, at the time of the survey lived outside big cities, and sometimes in areas where only a few gastroenterologists or other specialists are available. After diagnosis, most of the patients were in the follow-up of a specialist, however. In many cases, a specialist took part in the therapy in addition to the family or occupational doctors.

As IBD is a relatively rare disease that in many cases needs immunosuppressive therapy and regular laboratory and endoscopic examinations, it is logical that specialists be involved in treatment decisions. Even so, it is unclear, whether being in the follow-up under the care of a specialist improves HRQoL. The problem in interpreting this is that patients with the most severe disease usually remain under the care of specialists, whereas patients with non-problematic disease course are usually followed-up in primary care. In an UK community based study, being under specialist care was related to lower IBDQ scores (Rubin *et al* 2004). In the current study, patients who were followed-up at least in part by a specialist expressed significantly more often satisfaction with their current

therapy than those who were solely followed-up by occupational or family doctors. Despite this, no differences appeared in 15D or IBDQ scores between the groups.

Differences in treatment practices of IBD exist between different countries (Odes *et al* 2006). Compared to the earlier European EFCCA survey, Finnish patients used 5-ASA medication more frequently than did patients in the earlier study. 5-ASA appears to have a protective effect from CRC for both UC and colonic CD (Munkholm 2003, Winther *et al* 2004) but it has been rated no more effective than a placebo for active ileal CD (Dignass *et al* 2010). In the Finnish Current Care treatment guideline published in 2005, it is stated that 5-ASA is still a standard therapy for CD, which partly explains the common use of the medication. The use of immunomodulative and biological therapy was also more common in the current study, whereas rates of surgery for the CD patients were lower. Most patients reported an improved quality of life shortly after surgery, which is indicative of succesful patient selection for surgery. After the favourable situation immediately following surgery, recurrences of symptoms were common in the long run for both CD and UC patients. Maintaining postoperative remission in CD remains a challenge, even though novel therapies have reduced the rates of postoperative recurrencies (Regueiro *et al* 2009, Dignass *et al* 2010, Papay *et al* 2010). It has been reported that after IPAA surgery, chronic pouchitis and other pouch-related problems are common and can lead to the need for permanent ileostomy in 5% of the patients (Lepistö *et al* 2002, Cohen *et al* 2005).

Differences in treatment practices of IBD in different parts of Finland have been examined, as well. The rates of surgery varied somewhat between different university hospital districts, but otherwise treatment modalities, and also patient satisfaction were found to be equal (Haapamäki *et al* 2010).

The burden of IBD symptoms on the lives of patients and on society as a whole is remarkable. In spite of most patients being under the care of specialists, over one-third of the patients suffered from weekly IBD symptoms and many patients stated that the symptoms affected their capacity to work. A cost-analysis was not included in our survey, but in earlier surveys, a great amount of direct (hospitalizations, medications and surgery) and indirect costs (lost workdays, restricted activity days and early retirements) have been related to IBD, and these costs are higher in those with a more active disease (Gibson *et al* 2007). The mean annual costs of IBD vary considerably from country to country depending on the arrangement of therapy. In a European study, mean annual costs were 1524€ for UC and 2548€ for CD (Odes *et al* 2006). In the US, the annual costs were higher, $8265 (≈6140€) for CD and $5066 (≈3764€) for UC in 2008, and hospitalizations, medications and outpatient care were all attributable for about one-third of the costs (Kappelman *et al* 2008). Novel therapies, such as biological medications, have been found to improve the HRQoL and reduce resource use (Rubenstein *et al* 2002, Hanauer *et al* 2002) at least in the short term. Maintenance therapies that last under four years have been found to be cost-effective in selected CD patients (Bodger *et al* 2009). The additional costs caused by using biological medications in long maintenance therapies may exceed the conventional benchmarks for affordability. The problem with these models is the lack of real-patient data and lack of data of effect of infliximab on the long-term course of IBD (Bodger 2005).

6.3 Comorbidity (I, IV)

The self-reported rate of IBD patients for ankylosing spondylitis was 22 times higher and that of rheumatoid arthritis about three times higher than the corresponding values in the general population (Kaipiainen-Seppänen *et al* 1997, Aho *et al* 1998). Furthermore, the frequency of joint pain was remarkable. In addition to the impairment of HRQoL caused by these complaints, there are other problems related to joint and axial pain associated with IBD. The therapy of joint or axial pain in IBD patients may be problematic. Although the question about whether NSAIDs cause exacerbations of IBD is still unclear, in some cases at least their gastrointestinal and other side-effects can be detrimental to IBD patients (Feagins and Cryer 2010).

According to reliable data obtained from the Social Insurance Institution register, the prevalences of connective tissue diseases, asthma and obstructive pulmonary diseases, CHD, and pernicious anaemia were significantly higher for IBD patients than for their controls. However, regarding the diagnosis of pernicious anaemia in IBD patients, many of these patients are in fact CD sufferers who have undergone ileal resections that have led to a reduction in the absorption of vitamin B12.

Females with IBD appeared to be at increased risk for CHD compared to their non-IBD counterparts. The comparable risk for CHD in IBD males was only just significantly increased, but was still more than two-fold compared to female IBD patients, which indicates the much higher overall risk for CHD in males. In the national reimbursement register, 33 035 males aged 15-64 years have CHD, whereas the number is 9968 in females of the same age (a 3.3-fold difference). The difference between the older age cohorts is much smaller (Statistical Yearbook of the Social Insurance Institution 2009). IBD may contribute to the preterm development of CHD, although in this study no significant age difference was found between patients with both IBD and CHD and those patients with CHD alone. The use of acetylsalicylic acid preparations may have induced gastrointestinal bleeding leading to the discovery of earlier unsymptomatic or quiescent IBD in those patients initially diagnosed with CHD. Long-lasting and active IBD was a risk factor for CHD in both sexes. Chronic inflammation is suspected to accelerate atherosclerosis, and increased CHD risk has also been found in other inflammatory disorders, such as in rheumatoid arthritis (Sattar *et al* 2003, Snow and Mikuls 2005). However, in some studies no relationship between chronic inflammation and atherosclerosis has been determined after the appropriate corrections for known risk factors (Hansson 2005, Hamirani *et al* 2008). It is unfortunate, that no data on the smoking habits (or on lipid values) of our study subjects were available due to nature of the study.

The accuracy of IBD diagnoses in elderly patients with CHD needs to be considered. Ischaemic colitis has been suspected to be misdiagnosed as IBD on certain occasions (Brandt 2005). In such a case, one would expect the rate of CHD to be significantly higher in those patients diagnosed with IBD in their late middle age or in old age. However, no convincing evidence of this was found in our study.

6.4 Health-related quality of life and patient satisfaction (I, II, III, IV)

Disease activity was found to be the most important factor that predicted HRQoL, as noted in earlier studies (Irvine *et al* 1994, Casellas *et al* 2002, Guthrie *et al* 2002, Hjortswang *et al* 2003). The history of surgery was also related to both generic and disease-specific lower scores, which reflected the frequent postoperative recurrence of the disease and high reported rates of postoperative complications in study patients. The observed HRQoL of IPAA and stoma patients was lower than those reported by earlier surveys (Camilleri-Brennan *et al* 2003, Berndtsson *et al* 2007). Nevertheless, one must remember that those who had no problems may have considered it unnecessary to return the questionnaire. Disease activity probably also explains the lower HRQol scores for the newly-diagnosed patients. Another study on paediatric patients showed a similar result (Otley *et al* 2006), whereas in some other surveys a short disease duration was not associated with impaired HRQoL (Han *et al* 2005).

The differences in IBDQ scores of patients who receive different medications are mostly explained by the severity of the disease. Even the most effective and modern pharmaceutical preparations can not completely prevent the negative impact of disease on HRQoL. When compared to a placebo or to other medications, most of the medications currently in use have been shown to improve HRQoL (Feagan *et al* 2007a, Irvine *et al* 2008, Bastida *et al* 2010).

Despite the frequency of disturbing IBD symptoms, the great majority of patients expressed satisfaction with their current treatment. More patients in the current study were satisfied with their treatment than were found the in the other European countries (Ghosh and Mitchell 2007). The separate rates for each of the seven participating countries in that study have not been published. The sociodemographic characteristics of the patients, the local health care systems, and other conditions vary within and between different European countries, which is probably the main reason for the differences. Other reasons are the variation in accessibility to treatment and also the actual differences between treatment practices among the countries. However, the level of satisfaction expressed by the patients is indicative of good treatment practices in Finland.

The fact that 60% of the patients reported that their doctor never asked them about the impact of IBD symptoms on the quality of life is striking. Health care personnel often focus on reducing the actual disease symptoms, which indeed is one of the most important aspects in improving HRQoL. However, there are other important factors of HRQoL, such as psychological problems or comorbidity with other diseases, and their impacts can be difficult to detect by only looking at the patient's symptoms and objective medical findings.

In this survey, females reported worse disease-specific HRQoL than did males. This gender difference is a common finding in HRQoL studies, and the reason for it is mainly unresolved (Hunt and Annandale 1999, Guallar-Castillón *et al* 2005, Gallicchio *et al* 2007). Disease activity *per se* was not different between the sexes, but it is possible that

females experience symptoms of IBD as being more awkward and disturbing than do males.

15D appeared to be a feasible and applicable instrument for evaluating HRQoL in IBD patients. It had a ceiling effect of 6.2%, which is comparable or better than in other generic HRQoL tools. In a Finnish population sample, EQ-5D had a ceiling effect of 47% compared to 15% for 15D, which is indicative of the better discriminative power of 15D (Saarni *et al* 2006). 15D scores were more impaired with increasing age, which has also been reported in other 15D studies, and in studies that used other generic HRQoL instruments (Saarni *et al* 2006, Hopman *et al* 2009, Sørensen *et al* 2009). When compared to other studies of chronic conditions, the 15D scores of IBD patients have been similar to those of patients with epilepsy, diabetes-related complications, or anxiety (Stavem 1998, Hahl *et al* 2002, Pirkola *et al* 2009), but lower than those of patients who had undergone renal transplantation (Yildirim 2006).

6.5 Patient groups at risk of HRQoL impairment

The most striking impairment in HRQoL was seen in those patients with active, symptomatic disease. In addition, newly-diagnosed patients, many of whom were still having frequent IBD symptoms, and also older patients with increased rates of comorbid diseases had lower HRQoL scores. Perhaps surprisingly, HRQoL was impaired in patients who had undergone surgery, a feature very clearly observed in both CD patients and in UC patients after IPAA surgery. Similar to many other HRQoL studies, females in general had lower IBDQ scores than males. However, in this study, the generic 15D scores did not differ significantly between the sexes. Patients with comorbid diseases, or with extraintestinal manifestations of IBD, also had impaired HRQoL.

7 Conclusions

IBD is a chronic, relapsing disease that often occurs at a young age. It is common for IBD patients to have symptoms that affect leisure activities, work and their HRQoL. The frequency of symptoms was higher in Finnish IBD patients in this current study than in patients recruited in an earlier European study. Nevertheless, Finnish patients found their symptoms to be less disturbing, and the patients were more satisfied with their current therapy compared to the patients of the other European countries.

HRQoL has become an essential outcome of health care, though no gold standard for HRQoL exists. Generally, the use of both generic and disease-specific HRQoL instruments has been considered optimal in HRQoL assessment. In this study, both generic 15D and disease-specific IBDQ instruments were used.

Disease activity, as experienced by the patient, was the most important factor related to HRQoL. Of the demographic factors, older age, comorbid diseases, and female gender reduced the IBDQ scores. Other patient groups at risk of lower HRQoL were those with a newly-diagnosed disease and those with a history of surgery, especially after having had a stoma or an IPAA operation.

The generic 15D instrument appeared to be a feasible instrument for estimating the level of HRQoL in IBD. The 15D scores were significantly lower for IBD patients than for the general population sample. Active disease, older age and a history of surgery were associated with lower scores. IBDQ and 15D scores were strongly correlated in IBD patients, an observation that justifies the use of 15D as a fast and easily applied questionnaire for examining HRQoL of IBD patients.

The risks of many other chronic diseases, such as CHD, connective tissue diseases, asthma and chronic obstructive pulmonary diseases, were increased in IBD, and the comorbidities had a negative impact on the HRQoL. The increased prevalence of CHD in IBD encourages more efficacious management of other possible underlying cardiovascular risk factors (e.g. smoking and hypertension) and the inflammatory activity of IBD. The increased risk of preterm cardiovascular disease should be borne in mind especially in females. Furthermore, health-care personnel should be aware of the negative impact of comorbid diseases on the HRQoL of IBD patients.

HRQoL assessment helps to identify patients who need special support. With novel IBD therapies, symptoms and relapse rates of IBD are fewer for many patients. In such patients, the emphasis in examining the impact of the disease on their HRQoL should be directed at other areas in contrast to the approach that should be taken for patients with the active disease. Even when quiescent, the disease may have marked adverse impacts on the lives of the patients. Patients with an inactive disease often worry about the side-effects of medication, body-image issues, and the increased risks of surgery or of having cancer. The emphasis for patients with the inactive disease should be as much on addressing these issues than on easing individual IBD symptoms, especially in those patient groups that are prone to a low HRQoL. Correspondingly, for patients with the active disease, the main emphasis should be on ameliorating IBD symptoms and on improving various aspects of general well-being. These could be realised by therapeutic interventions to achieve improvement in both the patient's physical condition and his or her quality of life.

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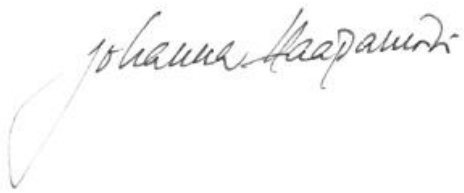

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References

Aamodt G, Jahnsen J, Bengtson M-B, Moum B, Vatn MH and the IBSEN Study Group. Geographic distribution and ecological studies of inflammatory bowel disease in southeastern Norway in 1990-1993. Inflamm Bowel Dis 2008;14:984-991.

Addolorato G, Capristo E, Stefanini GF, Gasbarrini G. Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. Scand J Gastroenterol 1997;32:1013-1021.

Afif W, Leighton JA, Hanauer SB, Loftus Jr EV, Faubion WA, Pardi DS, Tremaine WJ, Kane SV, Bruining DH, Cohen RD, Rubin DT, Hanson KA, Sandborn WJ. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. Inflamm Bowel Dis 2009;15:1302-1307.

Ahmad T, Armuzzi A, Bunce M, Mulcahy-Hawes K, Marshall SE, Orchard TR, Crawshaw J, Large O, de Silva A, Cook JT, Barnardo M, Cullen S, Welsh KI, Jewell DP. The molecular classification of the clinical manifestations of Crohn's disease. Gastroenterology 2002;122:854-866.

Aho K, Kaipiainen-Seppänen O, Heliövaara M, Klaukka T. Epidemiology of rheumatoid arthritis in Finland. Semin Arthritis Rheum 1998;27:325-334.

Al-Ghamdi AS, Al-Mofleh IA, Al-Rashed RS, Al-Amri SM, Aljebreen AM, Isnani AC, El-Badawi R. Epidemiology and outcome of Crohn's disease in a teaching hospital in Riyadh. World J Gastroenterol 2004;10:1341-1344.

Ali T, Lam D, Bronze MS, Humphrey MB. Osteoporosis in inflammatory bowel disease. Am J Med 2009;122:599-604.

Ananthakrishnan AN, Beaulieu DB, Ulistsky A, Zadvorovna Y, Skaros S, Johnson K, Naik A, Perera L, Issa M, Binion DG, Saeian K. Does primary sclerosing cholangitis impact quality of life in patients with inflammatory bowel disease? Inflamm Bowel Dis 2010;16:494-500.

Andersson P, Olaison G, Bendtsen P, Myrelid P, Sjödahl R. Health related quality of life in Crohn's proctocolitis does not differ from a general population when in remission. Colorect Dis 2003;5:56-62.

Andersson P, Söderholm JD. Surgery in ulcerative colitis: indication and timing. Dig Dis 2009;27:335-340.

Apajasalo M, Sintonen H, Holmberg C, Sinkkonen J, Aalberg V, Pihko H, Siimes MA, Kaitila I, Mäkelä A, Rantakari K, Anttila R, Rautonen J. Quality of life in early adolescence: a sixteen-dimensional health-related measure (16D). Qual Life Res 1996a; 5:205-211.

Apajasalo M, Rautonen J, Holmberg C, Sinkkonen J, Aalberg V, Pihko H, Siimes MA, Kaitila I, Mäkelä A, Erkkilä K, Sintonen H. Quality of life in pre-adolescence: a 17-dimensional health-related measure (17D). Qual Life Res 1996b; 5:532-538.

Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut 2006;55:47-53.

Aromaa A, Koskinen S. Health and functional capacity in Finland. Baseline results of the Health 2000 health examination survey. Publications of National Public Health Institute. Series B/2004:171.

Asakura K, Nishiwaki Y, Inoue N, Hibi T, Watanabe M, Takebayashi T. Prevalence of ulcerative colitis and Crohn's disease in Japan. J Gastroenterol 2009;44:659-665.

Baumgart DC, Carding SR. Inflammatory bowel disease : cause and immunobiology. Lancet 2007;369:1627-1640.

Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet 2007;369:1641-1657.

Baumgart DC, MacDonald JK, Feagan B. Tacrolimus (FK506) for induction of remission in refractory ulcerative colitis. Cochrane Database of Systematic Reviews 2008, Issue 3, Art No.: CD007216.

Bastida G, Nos P, Aguas M, Beltrán B, Iborra M, Ortiz V, Garrigues V, Estevan R, Ponce J. The effects of thiopurine therapy on health-related quality of life in inflammatory bowel disease. BMC Gastroenterol 2010;10:26-34.

Beaugerie L, Seksik P, Nion-Larmurier I, Gendre J-P, Cosnes J. Predictors of Crohn's disease. Gastroenterology 2006;130:650-656.

Bendix-Struve M, Bartels LE, Agnholt J, Dige A, Jørgensen SP, Dahlerup JF. Vitamin D3 treatment of Crohn's disease patients increases stimulated T cell IL-6 production and proliferation. Aliment Pharmacol Ther 2010; 32:1364-1372.

Ben-Horin S, Avidan B, Yanai H, Lang A, Chowers Y, Bar-Meir S. Familial clustering of Crohn's disease in Israel: prevalence and association with disease severity. Inflamm Bowel Dis 2009;15:171-175.

Berndtsson I, Lindholm E, Öresland T, Börjesson L. Long-term outcome after ileal pouch-anal anastomosis: function and health-related quality of life. Dis Colon Rectum 2007;50:1545-1552.

Bernklev T, Jahnsen J, Aadland E, Sauar J, Schulz T, Lygren I, Henriksen M, Stray N, Kjellevold O, Vatn M, Moum B. IBSEN Study Group. Health-related quality of life in patients with inflammatory bowel disease five years after the initial diagnosis. Scand J Gastroenterol 2004;39:365-373.

Bernklev T, Jahnsen J, Henriksen M, Lygren I, Aadland E, Sauar J, Schulz T, Vatn M, Moum B. Relationship between sick leave, unemployment, disability, and health-related quality of life in patients with inflammatory bowel disease. Inflamm Bowel Dis 2006;12:402-412.

Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol 2001a;96:1116-1122.

Bernstein CN, Blanchard JF, Kllewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease. A population-based study. Cancer 2001b;91:854-862.

Bernstein CN, Wajda A, Blanchard JF. The clustering of other inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology 2005;129:827-836.

Bernstein CN, Wajda A, Svenson LW, MacKenzie A, Koehoorn M, Jackson M, Fedorak R, Israel D, Blanchard JF. The epidemiology of inflammatory bowel disease in Canada: a population-based study. Am J Gastroenterol 2006;101:1559-1568.

Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. Clin Gastroenterol Hepatol 2008;6:41-45.

Biancone L, Michetti P, Travis S, Escher JC, Moser G, Forbes A, Hoffmann JC, Dignass A, Gionchetti P, Jantschek G, Kiesslich R, Kolacek S, Mitchell R, Panes J, Soderholm J, Vucelic B, Stange E for the European Crohn's and Colitis Organisation (ECCO). European evidence based consensus on the diagnosis and management of ulcerative colitis: special situations. J Crohn's Colitis 2008;2:63-92.

Bitton A, Sewitch MJ, Peppercorn MA, Edwardes MD, Shah S. Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. Am J Gastroenterol 2003;98:2203-2208.

Bjordal K. Impact of quality of life measurement in daily clinical practice. Ann Oncol 2004;15(suppl 4):279-282.

Black H, Mendoza M, Murin S. Thoracic manifestations of inflammatory bowel disease. Chest 2007;131:524-532.

Blondel-Kucharski F, Chiscop C, Marquis P, Cortot A, Baron F, Gendre J-P, Colombel J-F, and the Groupe d'Etudes Thérapeutique des Affections Inflammatoires Digestives (GETAID). Health-related quality of life in Crohn's disease: a prospective longitudinal study in 231 patients. Am J Gastroenterol 2001;96:2915-2920.

Bodger K. Economic implications of biological therapies for Crohn's disease. Review of infliximab. Pharmacoeconomics 2005;23:875-888.

Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. Aliment Pharmacol Ther 2009;30:265-274.

Borgaonkar MR, Irvine EJ. Quality of life measurement in gastrointestinal and liver disorders. Gut 2000;47:444-454.

Borgaonkar MR, Townson G, Donnelly M, Irvine EJ. Providing disease-related information worsens health-related quality of life in inflammatory bowel disease. Inflamm Bowel Dis 2002;8:264-269.

Bowling A. What things are important in people's lives? A survey of the public's judgements to inform scales of health related quality of life. Soc Sci Med 1995;41:1447-1462.

Brazier JE, Harper R, Jones NMB, O'Cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 1992;305:160-164.

Brandt LJ. Bloody diarrhea in an elderly patient. Gastroenterology 2005;128;157-63.

Brezenger N, Hartmann A, Strauch U, Schölmerich J, Andus T, Bollheimer LC. Increased insulin resistance and β cell activity in patients with Crohn's disease. Inflamm Bowel Dis 2006;12:53-56.

Brignola C, Cottone M, Pera A, Ardizzone S, Lia Scribano M, De Franchis R, D'Arienzo A, D'Albasio G, Pennestri D and the Italian Cooperative Study Group. Mesalamine in the prevention of endoscopic recurrence after intestinal resection for Crohn's disease. Gastroenterology 1995;108:345-349.

Brown SJ, Mayer L. The immune response in inflammatory bowel disease. Am J Gastroenterol 2007;102:2058-2069.

Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. Dig Dis Sci 1989;34:1841.1854.

Camilleri-Brennan J, Munro A, Steele RJC. Does an ileoanal pouch offer a better quality of life than a permanent ileostomy for patients with ulcerative colitis? J Gastrointest Surg 2003;7:814-819.

Canavan C, Abrams KR, Hawthorne B, Drossman D, Mayberry JF. Long-term prognosis in Crohn's disease: factors that affect quality of life. Aliment Pharmacol Ther 2006;23:377-385.

Carlsson E, Bosaeus I, Nordgren S. What concerns subjects with inflammatory bowel disease and an ileostomy? Scand J Gastroenterol 2003;38:978-984.

Casellas F, López-Vivancos J, Badia X, Vilaseca J, Malagelada J-R. Impact of surgery for Crohn's disease on health-related quality of life. Am J Gastroenterol 2000;95:177-182.

Casellas F, López-Vivancos J, Badia X, Vilaseca J, Malagelada J-R. Influence of inflammatory bowel disease on different dimensions of quality of life. Eur J Gastroenterol Hepatol 2001;13:567-572.

Casellas F, López-Vivancos J, Casado A, Malagelada J-R. Factors affecting health-related quality of life of patients with inflammatory bowel disease. Qual Life Res 2002;11:775-781.

Casellas F, Arenas JI, Baudet JS, Fábregas S, García N, Gelabert J, Medina C, Ochtorena I, Papo M, Rodrigo L, Malagelada J-R. Impairment of health-related quality of life in patients with inflammatory bowel disease: a Spanish multicenter study. Inflamm Bowel Dis 2005a;11:488-496.

Casellas F, López Vivancos J, Sampedro M, Malagelada J-R. Relevance of the phenotypic characteristics of Crohn's disease in patient perception of health-related quality of life. Am J Gastroenterol 2005b;100:2737-2742.

Cellier C, Sahmoud T, Froguel E, Adenis A, Belaiche J, Bretagne J-F, Florent C, Bouvry M, Mary J-Y, Modigliani R, and the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives (GETAID). Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. Gut 1994;35:231-235.

Cohen JL, Strong SA, Hyman NH, Buie WD, Dunn GD, Ko CY, Fleshner PR, Stahl TJ, Kim DG, Bastawrous AL, Perry WB, Cataldo PA, Rafferty JF, Ellis CN, Rakinic J, Gregorcyk S, Shellito PC, Kilkenny JW, Ternent CA, Koltun W, Tjandra JJ, Orsay CP, Whiteford MH, Penzer JR. Practice parameters for the surgical treatment of ulcerative colitis. Dis Colon Rectum 2005;48:1997-2009.

Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. Am J Gastroenterol 1999;94:1587-1592.

Cohen R, Robinson Jr D, Paramore C, Fraeman K, Renahan K, Bala M. Autoimmune disease concomitance among inflammatory bowel disease patients in the United States, 2001-2002. Inflamm Bowel Dis 2008;14:738-743.

Colombel J-F, Lémann M, Cassagnon M, Bouhnik Y, Duclos B, Dupas J-L, Notteghem B, Mary J-Y, and Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives (GETAID). A controlled trial comparing ciprofloxacin with mesalazine for the treatment of active Crohn's disease. Am J Gastroenterol 1999;94:674-678.

Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. Pharmacoeconomics 2000;17:13-35.

Cosnes J, Beaugerie L, Carbonnel F, Gendre J-P. Smoking cessation and the course of Crohn's disease: an intervention study. Gastroenterology 2001;120:1093-1099.

Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, Gendre J-P. Long-term evolution of disease behaviour of Crohn's disease. Inflamm Bowel Dis 2002;8:244-250.

Cosnes J, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre J-P. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. Gut 2005;54:237-241.

Cramer JA for the ILAE subcommission on outcome measurement of epilepsy. Principles of health-related quality of life: assessment in clinical trials. ILAE report. Epilepsia 2002;43:1084-1095.

Cregor JC, McDonald JWD, Klar N, Wall R, Atkinson K, Lamba B, Feagan BG. An evaluation of utility measurement in Crohn's disease. Inflamm Bowel Dis 1997;3:265-276.

Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis. A pathological and clinical entity. JAMA 1932;99:1323-1329.

Cullen G, O'Toole A, Keegan D, Sheahan K, Hyland JM, O'Donoghue DP. Long-term clinical results of ileocecal resection for Crohn's disease. Inflamm Bowel Dis 2007;13:1369-1373.

Dagli N, Poyrazoglu OK, Dagli AF, Sahbaz F, Karaca I, Kobat A, Bahcecioglu IH. Is inflammatory bowel disease a risk factor for early atherosclerosis? Angiology 2010;61:198-204.

Danese S, Papa A, Saibeni S, Repici A, Malesci A, Vecchi M. Inflammation and coagulation in inflammatory bowel disease: the clot thickens. Am J Gastroenterol 2007;102:174-186.

Daperno M, D'Haens G, van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary J-Y, Colombel J-F, Rutgeerts P. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505-512.

Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Econ 2004;13:437-452.

De Vos M. Review article: joint involvement in inflammatory bowel disease. Aliment Pharmacol Ther 2004 ;20(suppl 4):36-42.

D'Haens G, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, Lémann M, Marteau P, Rutgeerts P, Schölmerich J, Sutherland LR. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology 2007;132:763-786.

Dieckgraefe BK, Korzenik JR. Treatment af active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor. Lancet 2002;360:1478-1480.

Dignass AU, Baumgart DC, Sturm A. Review article: the aetiopathogenesis of inflammatory bowel disease – immunology and repair mechanisms. Aliment Pharmacol Ther 2004;20:9-17.

Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Öresland T, Windsor A, Stange EF, Travis SPL, for the European Crohn's and Colitis Organisation (ECCO). The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohn's Colitis 2010;4:28-62.

Domènech E, Zabana Y, Garcia-Planella E, López San Román A, Nos P, Ginard D, Gordillo J, Martínez-Silva F, Beltrán B, Mañosa M, Cabré E, Gassull MA. Clinical outcome of newly diagnosed Crohn's disease: a comparative, retrospective study before and after infliximab availability. Aliment Pharmacol Ther 2010;31:233-239.

Dorn SD, Sandler RS. Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: results from a systematic review and meta-analysis. Am J Gastroenterol 2007;102:662-667.

Drossman DA, Patrick DL, Mitchell CM, Zagami EA, Appelbaum MI. Health-related quality of life in inflammatory bowel disease. Functional status and patient worries and concerns. Dig Dis Sci 1989;34:1379-1386.

Drossman DA, Leserman J, Li Z, Mitchell CM, Zagami EA, Patrick DL. The rating form of IBD patient concerns: a new measure of health status. Psychosom Med 1991;53:701-712.

Dudley-Brown S, Nag A, Cullinan C, Ayers M, Hass S, Panjabi S. Health-related quality of life evaluation of Crohn's disease patients after receiving natalizumab therapy. Gastroenterol Nurs 2009;32:327-339.

Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526-535.

Ebrahim S. Clinical and public health perspectives and applications of health-related quality of life measurement. Soc Sci Med 1995;41:1383-1394.

Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. Part II: long-term prognosis. Gut 1963;4:309-315.

Farmer RG. Study of family history among patients with inflammatory bowel disease. Scand J Gastroenterol 1989;24(suppl 170):64-65.

Farrokhyar F, Marshall JK, Easterbrook B, Irvine EJ. Functional gastrointestinal disorders and mood disorders in patients with inactive inflammatory bowel disease: prevalence and impact on health. Inflamm Bowel Dis 2006;12:38-46.

Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GA, Gillies R, Hopkins M, Hanauer SB, McDonald JWD, for the North American Crohn's Study Group Investigators Methotrexate for the treatment of Crohn's disease. N Engl J Med 1995;332:292-297.

Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, Bala M, Johanns J, Olson A, Hanauer SB. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Am J Gastroenterol 2007a;102:794-802.

Feagan BG, Sandborn WJ, Hass S, Niecko T, White J. Health-related quality of life during natalizumab maintenance therapy for Crohn's disease. Am J Gastroenterol 2007b;102:2737-2746.

Feagan BG, Coteur G, Tan S, Keininger DL, Schreiber S. Clinically meaningful improvement in health-related quality of life in a randomized controlled trial of certolizumab pegol maintenance therapy for Crohn's disease. Am J Gastroenterol 2009;104:1976-1983.

Feagins LA, Cryer BL. Do non-steroidal anti-inflammatory drugs cause exacerbations in inflammatory bowel disease? Dig Dis Sci 2010;55:226-232

Ferguson A, Sedgwick DM, Drummond J. Morbidity of juvenile onset inflammatory bowel disease: effects on employment and education in early adult life. Gut 1994;35:665-668.

Ferrante M, Declerck S, De Hertogh G, Van Assche G, Geboes K, Rutgeerts P, Penninckx F, Vermeire S, D'Hoore A. Outcome after proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. Inflamm Bowel Dis 2008;14:20-28.

Fevery J, Verslype C, Lai G, Aerts R, Van Steenbergen W. Incidence, diagnosis, and therapy of cholangiocarcinoma in patients with primary sclerosing cholangitis. Dig Dis Sci 2007;52:3123-3135.

Fitzpatrick R, Fletcher A, Gore S, Jones D, Spiegelhalter D, Cox D. Quality of life measures in health care. I: applications and issues in assessment. BMJ 1992;305:1074-1077.

Flanagan JC. A research approach to improving our quality of life. Am Psychol 1978;33:138-147.

Friedman S, Blumberg RS. Inflammatory bowel disease; Etiology and pathogenesis. In: Fauci AS, Braunwald E, Kasper DL, et al. Harrison's principles of internal medicine, 17th ed. New York, NY, USA: MacGraw Hill. 2008.

Gallicchio L, Hoffman SC, Helzlsouer KJ. The relationship between gender, social support, and health-related quality of life in a community-based study in Washington County, Maryland. Qual Life Res 2007;16:777-786.

Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. BMJ 2002;324:14-17.

Gasche C, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine EJ, Jewell DP, Rachmilewitz D, Sachar DB, Sandborn WJ, Sutherland LR. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of gastroenterology, Vienna 1998. Inflamm Bowel Dis 2000;6:8-15.

Gaya DR, Russell RK, Nimmo ER, Satsangi J. New genes in inflammatory bowel disease: lessons for complex diseases? Lancet 2006;367:1271-1284.

Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. J Crohn's Colitis 2007;1:10-20.

Gibson PR, Weston AR, Shann A, Florin THJ, Lawrance IC, Macrae FA, Radford-Smith G. Relationship between disease severity, quality of life and health-care resource use in a cross-section of Australian patients with Crohn's disease. J Gastroenterol Hepatol 2007;22:1306-1312.

Gilson BS, Gilson JS, Bergner M, Bobbitt RA, Kressel S, Pollard WE, Vesselago M. The Sickness Impact profile. Development of an outcome measure of health care. Am J Public Health 1975;65:1304-1310.

Gisbert JP, Gomollón F. Common misconceptions in the diagnosis and management of anaemia in inflammatory bowel disease. Am J Gastroenterol 2008;103:1299-1307.

Gionchetti P, Rizzello F, Venturi A, Ferretti M, Brignola C, Miglioli M, Campieri M. Comparison of oral with rectal mesalazine in the treatment of ulcerative proctitis. Dis Colon Rectum 1998;41:93-97.

Gophna U, Sommerfeld K, Gophna S, Doolittle WF, Vedhuyzen van Zanten SJO. Differences between tissue-associated intestinal microfloras of patients with Crohn's disease and ulcerative colitis. J Clin Microbiol 2006;44:4136-4141.

Graff LA, Walker JR, Clara I, Lix L, Miller N, Rogala L, Rawsthorne P, Bernstein CN. Stress coping, distress, and health perceptions in inflammatory bowel disease and community controls. Am J Gastroenterol 2009;104:2959-2969.

Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson ABR, Williams CN, Nilsson L-G, Persson T, and the Canadian Inflammatory Bowel Disease Study Group. Oral budesonide for active Crohn's disease. N Engl J Med 1994;331:836-841.

Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson ABR, Williams CN, Nilsson L-G, Persson T, and the Canadian Inflammatory Bowel Disease Study Group. Oral budesonide as maintenance therapy for Crohn's disease: a placebo-controlled, dose-ranging study. Gastroenterology 1996;110:45-51.

Grossi E, Groth N, Mosconi P, Cerutti R, Pace F, Compare A, Apolone G. Development and validation of the short version of the Psychological General Well-Being Index (PGWB-S). Health Qual Life Outcomes 2006;4:88.

Guallar-Castillón P, Redondo Sendino Á, Banegas JR, López-García E, Rodríguez-Artalejo F. Differences in quality of life between women and men in the older population of Spain. Soc Sci Med 2005;60:1229-1240.

Guthrie E, Jackson J, Shaffer J, Thompson D, Tomenson B, Creed F. Psychological disorder and severity of inflammatory bowel disease predict health-related quality of life in ulcerative colitis and Crohn's disease. Am J Gastroenterol 2002;97:1994-1999.

Guyatt G, Mitcell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989;96:804-810.

Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Int Med 1993;118:622-629.

Gölder SK, Schreyer AG, Endlicher E, Feuerbach S, Schölmerich J, Kullman F, Seitz J, Rogler G, Herfarth H. Comparison of capsule endoscopy and magnetic resonance (MR) enteroclysis in suspected small bowel disease. Int J Colorectal Dis 2006;21:97-104.

Ha C, Magowan S, Accortt NA, Chen J, Stone CD. Risk of arterial thrombotic events in inflammatory bowel disease. Am J Gastroenterol 2009;104:1445-1451.

Haapamäki J, Roine RP, Turunen U, Färkkilä MA, Arkkila PET. Kroonista tulehduksellista suolistosairautta sairastavien elämänlaatu ja hoitokäytännöt. Suom Lääkäril 2010;65:599-604.

Hahl J, Hämäläinen H, Sintonen H, Simell T, Arinen S, Simell O. Health-related quality of life in type I diabetes without or with symptoms of long-term complications. Qual Life Res 2002;11:427-436.

Hamirani YS, Pandey S, Rivera JJ, Ndumele C, Budoff MJ, Blumenthal RS, Nasir K. Markers of inflammation and coronary artery calcification: a systematic review. Atherosclerosis 2008;201:1-7.

Hampe J, Cuthbert A, Croucher PJP, Mirza MM, Mascheretti S, Fisher S, Frenzel H, King K, Hasselmeyer A, MacPherson AJS, Bridger S, van Deventer S, Forbes A, Nikolaus S, Lennard-Jones JE, Foelsch UR, Krawczak M, Lewis C, Schreiber S, Mathew CG. Association between insertion mutation in NOD2 gene and Crohn's disease in German and British populations. Lancet 2001;357:1925-1928.

Han SW, Gregory W, Nylander D, Tanner A, Trewby P, Barton R, Welfare M. The SIBDQ: further validation in ulcerative colitis patients. Am J Gastroenterol 2000;95:145-151.

Han SW, McColl E, Barton JR, James P, Steen IN, Welfare MR. Predictors of quality of life in ulcerative colitis. The importance of symptoms and illness representations. Inflamm Bowel Dis 2005;11:24-34.

Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P, and the ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541-1549.

Hanauer SB, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. Clin Gastroenterol Hepatol 2004;2:379-388.

Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323-333.

Hansson GK. Mechanisms of disease: Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685-1695.

Hartman C, Eliakim R, Shamir R. Nutritional status and nutritional therapy in inflammatory bowel disease. World J Gastroenterol 2009;15:2570-2578.

Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514.

Haskell H, Andrews CW, Reddy SI, Dendrinos K, Farraye FA, Stucchi AF, et al. Pathologic significance of "backwash" ileitis in ulcerative colitis. Am J Gastroenterol 2005;29:1472-1481.

Heliö T, Halme L, Lappalainen M, Fodstad H, Paavola-Sakki P, Turunen U, Färkkilä M, Krusius T, Kontula K. CARD15/NOD2 gene variants are associated with familially occurring and complicated forms of Crohn's disease. Gut 2003;52:558-562.

Hemminki K, Li X, Sundquist K, Sundquist J. Familial association of inflammatory bowel diseases with other autoimmune and related diseases. Am J Gastroenterol 2010;105:139-147.

Henriksen M, Jahnsen J, Lygren I, Sauar J, Kjellevold Ø, Schulz T, Vatn MH, Moum B, and the IBSEN Study Group. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN Study). Inflamm Bowel Dis 2006a;12:543-550.

Henriksen M, Jahnsen J, Lygren I, Sauar J, Schulz T, Stray N, Vatn MH, Moum B, and the IBSEN Study Group. Change of diagnosis during the first five years after onset of inflammatory bowel disease: results of a prospective follow-up study (the IBSEN Study). Scand J Gastroenterol 2006b;41:1037-1043.

Hjortswang H, Järnerot G, Curman B, Sandberg-Gertzén H, Tysk C, Blomberg B, Almer S, Ström M. Validation of the Inflammatory Bowel Disease Questionnaire in Swedish patients with ulcerative colitis. Scand J Gastroenterol 2001;36:77-85.

Hjortswang H, Järnerot G, Curman B, Sandberg-Gertzén H, Tysk C, Blomberg B, Almer S, Ström M. The influence of demographic and disease-related factors on health-related quality of life in patients with ulcerative colitis. Eur J Gastroenterol Hepatol 2003;15:1011-1020.

Ho G-T, Chiam P, Drummond H, Loane J, Arnott DR, Satsangi J. The efficacy of corticosteroid therapy in inflammatory bowel disease: analysis of a 5-year UK inception cohort. Aliment Pharmacol Ther 2006;24:319-330.

Hopman WM, Harrison MB, Coo H, Friedberg E, Buchanan M, Van Den Kerkhof EG. Associations between chronic disease, age and physical and mental health status. Chronic Dis Can 2009;29:108-116.

Horsthuis K, Stokkers PCF, Stoker J. Detection of inflammatory bowel disease: diagnostic performance of cross-sectional imaging modalities. Abdom Imaging 2008;33:407-416.

Hugot JP, Laurent-Puig P, Gower-Rousseau C, Olson JM, Lee JC, Beaugerie L, Naom I, Dupas J-L, Van Gossum A, Weissenbach J, Mathew CG, Lennard-Jones JE, Cortot A, Colombel J-F, Gilles T. Mapping of a susceptibility locus for Crohn's disease on chromosome 16. Nature 1996;379:821-823.

Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel J-F, Sahbatou M, Thomas G. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 2001;411:599-603.

Hunt K, Annandale E. Relocating gender and morbidity: examining men's and women's health in contemporary Western societies. Introduction to special issue on gender and health. Soc Sci Med 1999;48:1-5.

Hunter JO. Is diet a factor in the pathogenesis of IBD? Inflamm Bowel Dis 2008;14:S35-S36.

Hyphantis TN, Tomenson B, Bai M, Tsianos E, Mavreas V, Creed F. Psychological distress, somatisation, and defense mechanisms associated with quality of life in inflammatory bowel disease patients. Dig Dis Sci 2010;55:724-732.

Höie O, Schouten LJ, Wolters FL, Solberg IC, Riis L, Mouzas IA, Politi P, Odes S, Langholz E, Vatn M, Stockbrügger RW, Moum B, on behalf of the European Collaborative Study Group of Inflammatory Bowel Disease (EC-IBD). Ulcerative colitis: no rise in mortality in a European-wide population based cohort 10 years after diagnosis. Gut 2007;56:497-503.

Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, Saibil F, McDonald JWD for the Canadian Crohn's Relapse Prevention Trial. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Gastroenterology 1994;106:287-296.

Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. J Clin Gastroenterol 1995;20:27-32.

Irvine EJ. Measuring quality of life: a review. Scand J Gastroenterol 1996;31(suppl 221):5-7.

Irvine EJ, Yeh C-H, Ramsey D, Stirling AL, Higgins PDR. The effect of mesalazine therapy on quality of life in patients with mildly and moderately active ulcerative colitis. Aliment Pharmacol Ther 2008;28:1278-1286.

Ishihara S, Aziz MM, Yuki T, Kazumori H, Kinoshita Y. Inflammatory bowel disease: review from the aspect of genetics. J Gastroenterol 2009;44:1097-1108.

Jahnsen J, Falch JA, Mowinckel P, Aadland E. Body composition in patients with inflammatory bowel disease: a population-based study. Am J Gastroenterol 2003;98:1556-1562.

Jenkins D, Balsitis M, Gallivan S, Dixon MF, Gilmour HM, Shepherd NA, Theodossi A, Williams GT. Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease. The British Society of Gastroenterology Initiative. J Clin Pathol 1997;50:93-105.

Jess T, Loftus Jr EV, Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, Schleck CD, Tremaine WJ, Melton LJ, Munkholm P, Sandborn WJ. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from Olmsted County, Minnesota. Gastroenterology 2006;130:1039-1046.

Järnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, Vilien M, Ström M, Danielsson Å, Verbaan H, Hellström PM, Magnuson A, Curman B. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005;128:1805-1811.

Kaipiainen-Seppänen O, Aho K, Heliövaara M. Incidence and prevalence of ankylosing spondylitis in Finland. J Rheumatol 1997;24:496-499.

Kappelman MD, Rifas-Shiman SL, Porter CQ, Ollendorf DA, Sandler RS, Galanko JA, Finkelstein JA. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. Gastroenterology 2008;135:1907-1913.

Katon W, Ciechanowski P. Impact of major depression on chronic medical illness. J Psychosom res 2002;53:859-863.

Katsanos KH, Vermeire S, Christodoulou DK, Riis L, Wolters F, Odes S, Freitas J, Hoie O, Beltrami M, Fornaciari G, Clofent J, Bodini P, Vatn M, Borralho Nunes P, Moum B, Munkholm P, Limonard C, Stockbrugger R, Rutgeerts P, Tsianos EV on behalf of the EC-IBD Study Group. Dysplasia and cancer in inflammatory bowel disease 10 years after diagnosis: results of a population-based European collaborative follow-up study. Digestion 2007;75:113-121.

Kelan sairausvakuutustilasto 2009. Kela 2010. www.kela.fi

Kim B, Barnett JL, Kleer CG, Appelman HD. Endoscopic and histological patchiness in treated ulcerative colitis. Am J gastroenterol 1999;94:3258-3262.

Kiran RP, Khoury W, Church JM, Lavery IC, Fazio VW, Remzi FH. Colorectal cancer complicating inflammatory bowel disease. Similarities and differences between Crohn's and ulcerative colitis based on three decades of experience. Ann Surg 2010;252:330-335.

Kirsner JB. Historical aspects of inflammatory bowel disease. J Clin Gastroenterol 1988;10:286-297.

Kolek A, Janout V, Tichý M, Grepl M. The incidence of inflammatory bowel disease is increasing among children 15 years old and younger in the Czech Republic. J Pediatr Gastroenterol Nutr 2004;38:362-3.

Konikoff MR, Denson LA. Role of fecal calprotectin as a biomarker of intestinal inflammation in inflammatory bowel disease. Inflamm Bowel Dis 2006;12:524-534.

Koutroubakis IE, Vlachonikolis IG. Appendectomy and the development of ulcerative colitis: results of a metaanalysis of published case-control studies. Am J Gastroenterol 2000;95:171-176.

Kurata JH, Kantor-Fish S, Frankl H, Godby P, Vadheim CM. Crohn's disease among ethnic groups in a large health maintenance organization. Gastroenterology 1992;102:1940-1948.

Kuriyama M, Kato J, Kuwaki K, Morimoto N, Nawa T, Fujimoto T, Kono H, Okano N, Miyaike J, Morita T, Okada H, Suzuki S, Yoshioka T, Shiode J, Suwaki K, Sakaguchi K, Shiratori Y, and for the Japan West Ulcerative Colitis Study Group. Clinical factors that impair health-related quality of life in ulcerative colitis patients vary with the disease duration. Eur J Gastroenterol Hepatol 2008;20:634-641.

Ladefoged K, Munck LK, Jorgensen F, Engel P. Skip inflammation of the appendiceal orifice: a prospective endoscopic study. Scand J Gastroenterol 2005;40:1192-1196.

Langholtz E, Munkholm P, Davidsen M, Nielsen OH, Binder V. Changes in extent of ulcerative colitis: a study on the course and prognostic factors. Scand J Gastroenterol 1996;31:260-266.

Langhorst J, Mueller T, Luedtke R, Franken U, Paul A, Michalsen A, Schedlowski M, Dobos GJ, Elsenbruch S. Effects of comprehensive lifestyle modification program on quality-of-life in patients with ulverative colitis; a twelve-month follow-up. Scand J Gastroenterol 2007;42:734-745.

Lapidus A. Crohn's disease in Stockholm County during 1990-2001. An epidemiological update. World J Gastroenterol 2006;12:75-81.

Larsson K, Sundberg Hjelm M, Karlbom U, Nordin K, Anderberg UM, Lööf L. A group-based patient education programme for high-anxiety patients with Crohn's disease or ulcerative colitis. Scand J Gastroenterol 2003;38:763-769.

Larsson K, Lööf L, Rönnblom A, Nordin K. Quality of life for patients with exacerbation in inflammatory bowel disease and how they cope with disease activity. J Psychosom Res 2008;64:139-148.

Leighton JA, Legnani P, Seidman EG. Role of capsule endoscopy in inflammatory bowel disease: where we are and where we are going. Inflamm Bowel Dis 2007;13:331-337.

Lennard-Jones JE, Shivananda S. Clinical uniformity of inflammatory bowel disease at presentation and during the first year of disease in the north and south of Europe. EC-IBD Study Group. Eur J Gastroenterol Hepatol 1997;9:353-359.

Leong RWL, Lau JY, Sung JJY. The epidemiology and phenotype of Crohn's disease in the Chinese population. Inflamm Bowel Dis 2004;10:646-651.

Lepistö A, Luukkonen P, Järvinen HJ. Cumulative failure rate of ileal pouch-anal anastomosis and quality of life after failure. Dis Colon Rectum 2002;45:1289-1294.

Lesage S, Zouali H, Cézard JP and the EPWG-IBD group, Colombel J-F and the EPIMAD group, Belaiche J and the GETAID group, Almer S, Tysk C, O'Morain C, Gassull M, Binder V, Finkel Y, Modigliani R, Gower-Rousseau C, Macry J, Merlin F, Chamaillard M, Jannot A-S, Thomas G, Hugot J-P. CARD15/NOD2 mutational analysis and genotype-phenotype correlation in 612 patients with inflammatory bowel disease. Am J Hum Genet 2002;70:845-857.

Levenstein S, Prantera C, Varvo V, Lia Scribano M, Andreoli A, Luzi C, Arcà M, Berto E, Milite G, Marcheggiano A. Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. Am J Gastroenterol 2000;95:1213-1220.

Levenstein S. Could stress play a role in IBD? Inflamm Bowel Dis 2008;14(Suppl 2):206-S207.

Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis 2008;14:1660-1666.

Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330:1841-1845.

Lindberg B, Persson B, Veress B, Ingelman-Sunberg H, Granqvist S. Twenty years' colonoscopic surveillance of patients with ulcerative colitis. Detection of dysplastic and malignant transformation. Scand J Gastroenterol 1996;31:1195-1204.

Lindqvist B, Benito de Valle M, Gullberg B, Björnsson E. Incidence and prevalence of primary sclerosing cholangitis in a defined adult population in Sweden. Hepatology 2010;52:571-577.

Lix LM, Graff LA, Walker JR, Clara I, Rawsthorne P, Rogala L, Miller N, Ediger J, Pretorius T, Bernstein CN. Longitudinal study of quality of life and psychological functioning for active, fluctuating, and inactive disease patterns in inflammatory bowel disease. Inflamm Bowel Dis 2008;14:1575-1584.

Loftus CG, Loftus EV, Harmsen WS, Zinsmeister AR, Tremaine WJ, Melton LJ, Sandborn WJ. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota 1940-2000. Inflamm Bowel Dis 2007;13:254-261.

Loftus EV Jr, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. Gut 2000;46:336-343.

Loftus EV. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 2004;126:1504-1517.

Loftus EV, Feagan BG, Colombel J-F, Rubin DT, Wu EQ, Yu AP, Pollack PF, Chao J, Mulani P. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. Am J Gastroenterol 2008;103:3132-3141.

MacFaul GR, Chapman RW. Sclerosing cholangitis. Curr Opin Gastroenterol 2004;20:275-280.

Maconi G, Imbesi V, Bianchi Porro G. Doppler ultrasound measurement of intestinal blood flow in inflammatory bowel disease. Scand J Gastroenterol 1996;31:590-593.

Mahadeva R, Walsh G, Flower CDR, Shneerson JM. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. Eur Respirator J 2000; 15 :41-48.

Malaty HM, Fan X, Opekun AR, Thibodeaux C, Ferry GD. Rising incidence of inflammatory bowel disease among children; a 12-year study. J Pediatr gastroenterol Nutr 2010;50:27-31.

Manichanh C, Rigottier-Gois L, Bonnaud E, Gloux K, Pelletier E, Frangeul L, Nalin R, Jarrin C, Chardon P, Marteau P, Roca J, Dore J. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. Gut 2006;55:205-211.

Manninen P, Karvonen A-L, Huhtala H, Rasmussen M, Collin P. The epidemiology of inflammatory bowel diseases in Finland. Scand J Gastroenterol 2010;45:1063-1067.

Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Group d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut 1989 ;30 :983-989.

Masala G, Bagnoli S, Ceroti M, Saieva C, Trallori G, Zanna I, d'Albasio G, Palli D. Divergent patterns of total and cancer mortality in ulcerative colitis and Crohn's disease patients: the Florence IBD study 1978-2001. Gut 2004;53:1309-1313.

Mayer L. Evolving paradigms in the pathogenesis of IBD. J Gastroenterol 2010;45:9-16.

McCarthy D, Duggan P, O'Brien M, Kiely M, McCarthy J, Shanahan F, Cashman KD. Seasonality of vitamin D status and bone turnover in patients with Crohn's disease. Aliment Pharmacol Ther 2005;21:1073-1083.

McLeod RS, Lavery IC, Leatherman JR, Maryland PA, Fazio VW, Jagelman DG, Weakley FL. Factors affecting quality of life with a conventional ileostomy. World J Surg 1986;10:474-480.

Miehsler W, Reinisch W, Valic E, Osterode W, Tillinger W, Feichtenschlager T, Grisar J, Machold K, Scholz S, Vogelsang H, Novacek G. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? Gut 2004;53:542-548.

Miehsler W, Weichselberger M, Öfferlbauer-Ernst A, Dejaco C, Reinisch W, Vogelsang H, Machold K, Stamm T, Gangl A, Moser G. Which patients with IBD need psychological interventions? A controlled study. Inflamm Bowel Dis 2008;14:1273-1280.

Mili F, Helmick CG, Zack MM, Moriarty DG. Health related quality of life among adults reporting arthritis: analysis of data from the behavioral risk factor surveillance system, US, 1996-99. J Rheumatol 2003;30:160-166.

Mitchell A, Guyatt G, Singer J, Irvine EJ, Goodacre R, Tompkins C, Williams N, Wagner F. Quality of life in patients with IBD. J Clin Gastroenterol 1988;10:306-310.

Mittermaier C, Dejaco C, Waldhoer T, Oefferlbauer-Ernst A, Miehsler W, Beier M, Tillinger W, Gangl A, Moser G. Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. Psychosom Med 2004;66:79-84.

Moreno-Jiménez B, López Blanco B, Rodríguez-Muñoz A, Garrosa Hernández E. The influence of personality cofactors on health-related quality of life of patients with inflammatory bowel disease. J Psychosom Res 2007;62:39-46.

Moskovitz DN, Van Assche G, Maenhout B, Arts J, Ferrante M, Vermeire S, Rutgeerts P. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. Clin Gastroenterol Hepatol 2006;4:760-765.

Moum B, Ekbom A, Vatn MH, Elgjo K. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. Am J Gastroenterol 1999;94:1564-1569.

Muennig P. Working with quality of life measures. In: Designing and conducting cost-effectiveness analyses in medicine and health care. 1st ed. San Francisco, Ca, USA: Jossey-Bass; 2002: 190-202.

Munkholm P. Review article: the incidence and prevalence of colorectal cancer in inflammatory bowel disease. Aliment Pharmacol Ther 2003;18 (Suppl 2):1-5.

Mussell M, Böcker U, Nagel N, Olbrich R, Singer MV. Reducing psychological distress in patients with inflammatory bowel disease by cognitive-behavioural treatment: exploratory study of effectiveness. Scand J Gastroenterol 2003;38:755-762.

Nell S, Suerbaum S, Josenhans C. The impact of the microbiota on the pathogenesis of IBD: lessons from mouse infection models. Nature reviews. Microbiology 2010;8:564-577.

Ng SC, Plamondon S, Gupta A, Burling D, Kamm MA. Prospective assessment of the effect on quality of life of anti-tumour necrosis factor therapy for perineal Crohn's fistulas. Aliment Pharmacol Ther 2009;30:757-766.

Nguyen GC, Torres EA, Regueiro M, Bromfield G, Bitton A, Stempak J, Dassopoulos T, Schumm P, Gregory FJ, Griffiths AM, Hanauer SB, hanson J, Harris ML, Kane SV, Kiraly Orkwis H, Lahaie R, Oliva-Hemker M, Pare P, Wild GE, Rioux JD, Yang H, Duerr RH, Cho JH, Steinhart AH, Brant SR, Silverberg MS. Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic whites: characterization of a large North American cohort. Am J Gastroenterol 2006;101:1012-1023.

Nicholas DB, Swan SR, Gerstle TJ, Allan T, Griffiths AM. Struggles, strengths, and strategies: an ethnographic study exploring the experiences of adolescents living with an ostomy. Health Qual Life Outcomes 2008;6:114.

Nikolaus S, Schreiber S. Diagnostics of inflammatory bowel disease. Gastroenterology 2007;133:1670-1689.

Niv Y, Abuksis G, Frase GM. Epidemiology of ulcerative colitis in Israel: a survey of Israeli kibbutz settlements. Am J Gastroenterol 2000;95:693-698.

Nordin K, Påhlman L, Larsson K, Sundberg-Hjelm M, Lööf L. Health-related quality of life and psychosocial distress in a population-based sample of Swedish patients with inflammatory bowel disease. Scand J Gastroenterol 2002;37:450-457.

North CS, Alpers DH, Helzer JE, Spitznagel L, Clouse RE. Do life events or depression exacerbate inflammatory bowel disease? Ann Intern Med 1991;114:381-386.

Odes S, Vardi H, Friger M, Wolters F, Russel MG, Riis L, Munkholm P, Politi P, Tsianos E, Clofent J, Vermeire S, Monteiro E, Mouzas I, Fornaciari G, Sijbrandij J, Limonard C, van Zeijl G, O'Morain C, Moum B, Vatn M, Stockbrugger R, on behalf of the European Collaborative Study on Inflammatory Bowel Disease. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. Gastroenterology 2006;131:719-728.

Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar J-P, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nuñez G, Cho JH. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001;411:603-606.

Otley AR, Griffiths AM, Hale S, Kugathasan S, Pfefferkorn M, Mezoff A, Rosh J, Tolia V, Markowitz J, Mack D, Oliva-Hemker M, Wyllie R, Rothbaum R, Bousvaros A, Del Rosario F, Evans J, Blanchard W, Hyams J, for the Pediatric IBD Collaborative Research Group. Health-related quality of life in the first year after a diagnosis of pediatric inflammatory bowel disease. Inflamm Bowel Dis 2006;12:684-691.

Ott SJ, Musfeldt M, Wenderoth DF, Hampe J, Brant O, Fölsch UR, Timmis KN, Schreiber S. Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. Gut 2004;53:685-693.

Ott SJ, Plamondon S, Hart A, Begun A, Rehman A, Kamm MA, Schreiber S. Dynamics of the mucosa-associated flora in ulcerative colitis patients during remission and clinical relapse. J Clin Micriobiol 2008;46:3510-3513.

Oxelmark L, Magnusson A, Löfberg R, Hillerås P. Group-based intervention program in inflammatory bowel disease patients: effects on quality of life. Inflamm Bowel Dis 2007;13:182-190.

Pace F, Molteni P, Bollani S, Sarzi-Puttini P, Stockbrügger R, Bianchi Porro G, Drossman DA. Inflammatory bowel disease versus irritable bowel syndrome; a hospital-based, case-control study of disease impact on quality of life. Scand J Gastroenterol 2003;38:1031-1038.

Pallis AG, Vlachonikolis IG, Mouzas IA. Quality of life of Greek patients with inflammatory bowel disease. Validation of the Greek version of the Inflammatory Bowel Disease Questionnaire. Digestion 2001;63:240-246.

Palm Ø, Bernklev T, Moum B, Gran JT. Non-inflammatory joint pain in patients with inflammatory bowel disease is prevalent and has a significant impact on health-related quality of life. J Rheumatol 2005;32:1755-1759.

Papa A, Santoliquido A, Danese S, Covino M, Di Campli C, Urgesi R, Grillo A, Guglielmo S, Tondi P, Guidi L, De Vitis I, Fedeli G, Gasbarrini G, Gasbarrini A. Increased carotid intima-media thickness in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2005;22:839-846.

Papay P, Reinisch W, Ho E, Gratzer C, Lissner D, Herkner H, Riss S, Dejaco C, Miehsler W, Vogelsang H, Novacek G. The impact of thiopurines on the risk of surgical recurrence in patients with Crohn's disease after first intestinal surgery. Am J Gastroenterol 2010;105:1158-1164.

Pardi DS, Sandborn WJ. Systematic review: the management of pouchitis. Aliment Pharmacol Ther 2006;23:1087-1096.

Parente F, Greco S, Molteni M, Cucino C, Maconi G, Sampietro GM, Danelli PG, Cristaldi M, Bianco R, Gallus S, Bianchi Porro G. Role of early ultrasound in detecting

inflammatory intestinal disorders and identifying their anatomical location within the bowel. Aliment Pharmacol Ther 2003;18:1009-1016.

Parsi MA, Achkar J-P, Richardson S, Katz J, Hammel JP, Lashner BA, Brzezinski A. Predictors of response ti infliximab in patients with Crohn's disease. Gastroenterology 2002;123:707-713.

Patel V, MacDonald JK, McDonald JWD, Chande N. Methotrexate for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2009, Issue 4, Art No.: CD006884.

Penna C, Dozois R, Tremaine W, Sandborn W, LaRusso N, Scleck C, Ilstrup D. Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. Gut 1996;38:234-239.

Penner RM, Madsen KL, Fedorak RN. Postoperative Crohn's disease. Inflamm Bowel Dis 2005;11:765-777.

Pizzi LT, Weston CM, Goldfarb NI, Moretti D, Cobb N, Howell JB, Infantolino A, DiMarino AJ, Cohen S. Impact of chronic conditions on quality of life in patients with inflammatory bowel disease. Inflamm Bowel Dis 2006;12:47-52.

Polito JM, Childs B, Mellits ED, Tokayer AZ, Harris ML, Bayless TM. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. Gastroenterology 1996;111:580-586.

Prefontaine E, MacDonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2010, Issue 6, Art No.: CD000545.

Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJH. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398-1405.

Price AB. Overlap in the spectrum of non-specific inflammatory bowel disease – "colitis indeterminate". J Clin Pathol 1978;31:567-577.

Radlmayr M, Torok HP, Martin K, Folwaczny C. The c-insertion mutation of the NOD2 gene is associated with fistulising and fibrostenotic phenotypes in Crohn's disease. Gastroenterology 2002;122:2091-2092.

Raisch DW. Understanding quality-adjusted life years and their application to pharmacoeconomic research. Ann Pharmacother 2000;34:906-914.

Rajwal SR, Puntis JWL, McClean P, Davison SM, Newell SJ, Sugarman I, Stringer MD. Endoscopic rectal sparing in children with untreated ulcerative colitis. J Pediatr Gastroenterol Nutr 2004;38:66-69.

Rao SS, Holdsworth CD, Read NW. Symptoms and stool patterns in patients with ulcerative colitis. Gut 1988;29:342-345.

Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, Harrison J, Plevy SE. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009;136:441-450.

Rehman A, Lepage P, Nolte A, Hellmig S, Schreiber S, Ott SJ. Transcriptional activity of the dominant gut mucosal microbiota in chronic inflammatory bowel disease patients. J Med Microbiol 2010;59:1114-1122.

Reinisch W, Sandborn WJ, Bala M, Yan S, Feagan BG, Rutgeerts P, Radford-Smith G, Xu S, Eisenberg D, Olson A, Colombel J-F. Response and remission are associated with improved quality of life, employment and disability status, hours worked, and productivity of patients with ulcerative colitis. Inflamm Bowel Dis 2007;13:1135-1140.

Rieber A, Wruk D, Potthast S, Nüssle K, Reinshagen M, Adler G, Brambs H-J. Diagnostic imaging in Crohn's disease: comparison of magnetic resonance imaging and conventional imaging methods. Int J Colorectal Dis 2000;15:176-181.

Rubenstein JH, Chong RY, Cohen RD. Infliximab decreases resource use among patients with Crohn's disease. J Clin Gastroenterol 2002;35:151-156.

Rubin GP, Hungin APS, Chinn DJ, Dwarakanath D. Quality of life in patients with established inflammatory bowel disease: a UK general practice survey. Aliment Pharmacol Ther 2004;19:529-535.

Russel MGVM, Volovics A, Schoon EJ, van Wijlick EHJ, Logan RF, Shivananda S, Stockbrügger RW, and the European Collaborative IBD Study Group. Inflammatory bowel disease: is there any relation between smoking status and disease presentation? Inflamm Bwel Dis 1998;4:182-186.

Russel RK, Satsangi J. IBD: a family affair. Best Pract Res Clin Gastroenterol 2004;18:525-539.

Rutgeerts P, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. Gut 1984;25:665-672.

Rutgeerts P, Van Assche G, Vermeire S. Optimizing anti-TNF treatment in inflammatory bowel disease. Gastroenterology 2004;126:1593-1610.

Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJS, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462-2476.

Rutgeerts P, Schreiber S, Feagan B, Keininger DL, O'Neil L, Fedorak RN. Certolizumab pegol, a monthly subcutaneously administered Fc-free anti-TNFα, improves health-related quality of life in patients with moderate to severe Crohn's disease. Int J Colorect Dis 2008;23:289-296.

Saarni S, Härkänen T, Sintonen H, Suvisaari J, Koskinen S, Aromaa A, Lönnqvist J. The impact of 29 chronic conditions on health related quality of life: a general population survey in Finland using 15D and EQ-5D. Qual Life Res 2006;15:1403-1414.

Saich R, Chapman R. Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease. World J Gastroenterol 2008;14:331-337.

Sajid MS, Tonsi A, Baig MK. Health-related quality of life measurement. Int J Health Care 2008;21:365-373.

Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, Panaccione R, Wolf D, Kent JD, Bittle B, Li J, Pollack PF. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007;56:1232-1239.

Sappati Biyyani RSR, Fahmy NM, Baum E, Nelson KM, King JF. Inflammatory bowel disease and coronary artery disease. Indian J Gastroenterol 2009;28:28-30.

Satsangi J, Silverberg MS, Vermeire S, Colombel J-F. The Montreal classification of inflammatory bowel disease: controversies, consensus and implications. Gut 2006;55:749-753.

Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003;108:2957-2963.

Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1987;317:1625-1629.

Schwartz DA, Loftus EV, Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of fistulising Crohn's disease in Olmsted County, Minnesota. Gastroenterology 2002;122:875-880.

Scott KM, Bruffaerts R, Tsang A, Ormel J, Alonso J, Angermeyer MC, Benjet C, Bromet E, de Girolamo G, de Graaf R, Gasquet I, Gureje O, Haro JM, He Y, Kessler RC, Levinson D, Mneimneh ZN, Oakley Browne MA, Posada-Villa J, Stein DJ, Takeshima T, Von Korff M. Depression-anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. J Affect Disord 2007;103:113-120.

Shen W, Durum SK. Synergy of IL-23 and Th17 cytokines: new light on inflammatory bowel disease. Neurochem Res 2010;35:940-946.

Silverberg MS, Satsangi J, Ahmad T, Arnott IDR, Bernstein CN, Brant SR, Caprilli R, Colombel J-F, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV Jr, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19:5-36.

Sintonen H. The 15D-measure of health-related quality of life. Reliability, validity and sensitivity of its health state descriptive system. National Centre for Health Program Evaluation, Working Paper 41, Melbourne 1994 (http://www.buseco.monash.edu.au/centres/che/pubs/wp41.pdf).

Sintonen H. The 15D instrument of health-related quality of life: properties and applications. Ann Med 2001;33:328-336.

Sipponen T, Kärkkäinen P, Savilahti E, Kolho K-L, Nuutinen H, Turunen U, Färkkilä M. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. Aliment Pharmacol Ther 2008;28:1221-1229.

Snow MH, Mikuls TR. Rheumatoid arthritis and cardiovascular disease: the role of systemic inflammation and evolving strategies of prevention. Curr Opin Rheumatol 2005 ;17:234-241.

Solberg IC, Vatn MH, Høie O, Stray N, Sauar J, Jahnsen J, Moum B, Lygren I, and the IBSEN Study Group. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol 2007;5:1430-1438.

Solberg IC, Lygren I, Jahnsen J, Aadland E, Høie O, Cvancarova M, Bernklev T, Henriksen M, Sauar J, Vatn MH, Moum B and the IBSEN Study Group. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol 2009;44:431-440.

Sonnenberg A, McCarty DJ, Jacobsen SJ. Geographic variation of inflammatory bowel disease within the United States. Gastroenterology 1991;100:143-149.

Sørensen J, Davidsen M, Gudex C, Møller Pedersen K, Brønnum-Hansen H. Danish EQ-5D population norms. Scand J Public Health 2009;37:467-474.

Sostegni R, Daperno M, Scaglione N, Lavagna A, Rocca R, Pera A. Review article: Crohn's disease: monitoring disease activity. Aliment Pharmacol Ther 2003;17(suppl 2):11-17.

Stange EF, Travis SPL, Vermeire S, Reinisch W, Geboes K, Barakauskiene A, Feakins R, Fléjou JF, Herfarth H, Hommes DW, Kupcinskas L, Lakatos PL, Mantzaris GJ, Schreiber S, Villanacci V, Warren BF for the European Crohn's and Colitis Organisation (ECCO). European evidence-based consensus on the diagnosis and management of ulcerative colitis: definitions and diagnosis. Journal of Crohn's and colitis 2008. 2:1-23.

Statistical Yearbook of the Social Insurance Institution 2008. Vammala, Finland: Kela ;2009.

Statistical Yearbook of the Social Insurance Institution 2010. Vammala, Finland: Kela ;2011.

Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 4, Art No.: CD000301.

Stewart AL, Hays RD, Ware JE Jr. The MOS Short-Form General Health Survey. Reliability and validity in a patient population. Med Care 1988;26:724-735.

Stjernman H, Grannö C, Bodemar G, Järnerot G, Ockander L, Tysk C, Blomberg B, Almer S, Ström M, Hjortswang H. Evaluation of the Inflammatory Bowel Disease Questionnaire in Swedish patients with Crohn's disease. Scand J Gastroenterol 2006;41:934-943.

Stjernman H, Tysk C, Almer S, Ström M, Hjortswang H. Worries and concerns in a large unselected cohort of patients with Crohn's disease. Scand J Gastroenterol 2010;45:696-706.

Tamboli CP, Neut C, Desreumaux P, Colombel JF. Dysbiosis in inflammatory bowel disease. Gut 2004;53:1-4.

Targan SR, Hanauer SB, van Deventer SJH, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ, for the Crohn's Disease cA2 Study Group. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. N Engl J Med 1997;337:1029-1035.

The IBD in EPIC Study Investigators. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case-control study within a European prospective cohort study. Gut 2009;58:1606-1611.

Thorlacius H, Toth E. Role of chromoendoscopy in colon cancer surveillance in inflammatory bowel disease. Inflamm Bowel Dis 2007;13:911-917.

Tibble J, Teahon K, Thjodleifsson B, Roseth A, Sigthorsson G, Bridger S, Foster R, Sherwood R, Fagerhol M, Bjarnason I. A simple method for assessing intestinal inflammation in Crohn's disease. Gut 2000;47:505-513.

Tillinger W, Mittermaier C, Lochs H, Moser G. Health-related quality of life in patients with Crohn's disease. Influence of surgical operation – a prospective trial. Dig Dis Sci 1999;44:932-938.

Travis SPL, farrant JM, Ricketts C, Mortensen NM, Kettlewell MGW, Jewell DP. Predicting outcome in severe ulcerative colitis. Gut 1996;38:905-910.

Travis SPL, Stange EF, Lémann M, Øresland T, Bemelman WA, Chowers Y, Colombel J-F, D-Haens G, Ghosh S, Marteau P, Kruis W, Mortensen NJ, Penninckx F, Gassull M for the European Crohn's and Colitis organisation (ECCO). European evidence based consensus on the diagnosis and management of ulcerative colitis: current management. J Crohn's Colitis 2008;2:24-62.

Truelove SC, Witts LJ. Cortisone in ulcerative colitis. Final report on a therapeutic trial. BMJ 1955;2:1041-1048.

Turina M, Pennington CJ, Kimberling J, Stromberg AJ, Petras RE, Galandiuk S. Chronic pouchitis after ileal pouch-anal anastomosis for ulcerative colitis: effect on quality of life. J Gastrointest Surg 2006;10:600-606.

Turunen P, Kolho K-L, Auvinen A, Iltanen S, Huhtala H, Ashorn M. Incidence of inflammatory bowel disease in Finnish children, 1987-2003. Inflamm Bowel Dis 2006;12:677-683.

Turner D, Seow CH, Greenberg GR, Griffiths AM, Silverberg MS, Steinhart AH. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. Clin Gastroenterol Hepatol 2009;7:1081-1088.

Tysk C, Lindberg E, Järnerot G, Floderus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and influence of smoking. Gut 1988;29:990-996.

Van Assche G, D'Haens G, Noman M, Vermeire S, Hiele M, Asnong K, Arts J, D'Hoore A, Penninckx F, Rutgeerts P. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology 2003;125:1025-1031.

Van Assche G, Dignass A, Panes J, Beaugerie L, Kragiannis J, Allez M, Ochsenkühn T, Orchard T, Rogler G, Louis E, Kupcinskas L, Mantzaris G, Travis S, Stange E, for the European Crohn's and Colitis Organisation (ECCO). The second European evidence-based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. J Crohn's Colitis 2010a;4:7-27.

Van Assche G, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, Guslandi M, Oldenburg B, Dotan I, Marteau P, Ardizzone A, Baumgart DC, D'Haens G, Gionchetti P, Portela F, Vucelic B, Söderholm J, Escher J, Koletzko S, Kolho K-L, Lukas M, Mottet C, Tilg H, Vermeire S, Carbonnel F, Cole A, Novacek G, Reinshagen M, Tsianos E, Herrlinger K, Oldenburg B, Bouhnik Y, Kiesslich R, Stange E, Travis S, Lindsay J, for the European Crohn's and Colitis Organisation (ECCO). The second European evidence-based consensus on the diagnosis and management of Crohn's disease: special situations. J Crohn's Colitis 2010b;4:63-101..

Van Balkom BPJ, Schoon EJ, Stockbrügger RW, Wolters FL, van Hogezand RA, van Deventer SJH, Oldenburg B, van Dullemen HM, Russel MGVM. Effects of anti-tumour necrosis factor-α therapy on the quality of life in Crohn's disease. Aliment Pharmacol Ther 2002;16:1101-1107.

Van Oostayen JA, Wasser MN, van Hogezand RA, Griffioen G, de Roos A. Activity of Crohn's disease assessed by measurement of superior mesenteric artery flow with Doppler US. Radiology 1994;193:551-554.

Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. Inflamm Bowel Dis 2004;10:661-665.

Vidal À, Gómez-Gil E, Sans M, Portella MJ, Salamero M, Piqué M, Panés J. Health-related quality of life in inflammatory bowel disease patients: the role of psychopathology and personality. Inflamm Bowel Dis 2008;14:977-983.

Vind I, Riis L, Knudsen E, Pedersen N, Elkjaer M, Bak Andersen I, Wewer V, Nørregaard P, Moesgaard F, Bendtsen F, Munkholm P, and the DCCD Study Group. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County 2003-2005: a population-based study from the Danish Crohn colitis database. Am J Gastroenterol 2006;101:1274-1282.

Wakefield AJ, Dhillon AP, Rowles PM, Sawyerr AM, Pittilo RM, Lewis AM, Pounder RE. Pathogenesis of Crohn's disease: multifocal gastrointestinal infarction. Lancet 1989;2:1057-1062.

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483.

Watanabe K, Funayama Y, Fukushima K, Shibata C, Takahashi K-I, Ogawa H, Haneda S, Kudo K, Kohyama A, Sasaki I. Assessment of the Japanese inflammatory bowel disease questionnaire in patients after ileal pouch anal anastomosis for ulcerative colitis. J Gastroenterol 2006;41:662-667.

Wehkamp J, Schmid M, Stange E. Defensins and other antimicrobial peptides in inflammatory bowel disease. Curr Opin Gastroenterol 2007;23:370-378.

Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. JAMA 1995;273:59-65.

Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. Clin Gastroenterol Hepatol 2004;2:1088-1095.

Wolters FL, Russel MG, Sijbrandij J, Schouten LJ, Odes S, Riis L, Munkholm P, Langholz E, Bodini P, O'Morain C, Katsanos K, Tsianos E, Vermeire S, van Zeijl G, Limonard C, Hoie O, Vatn M, Moum B, Stockbrügger RW on behalf of the European Collaborative Study Group on Inflammatory Bowel Disease (EC-IBD). Disease outcome of inflammatory bowel disease patients: general outline of a Europe-wide population-based 10-year clinical follow-up study. Scand J Gastroenterol 2006a;41:46.54.

Wolters FL, Russel MG, Sijbrandij J, Schouten LJ, Odes S, Riis L, Munkholm P, Bodini P, O'Morain C, Mouzas IA, Tsianos E, Vermeire S, Monteiro E, Limonard C, Vatn M, Fornaciari G, Pereira S, Moum B, Stockbrügger RW, on behalf of the European Collaborative Study Group on Inflammatory Bowel Disease (EC-IBD). Crohn's disease: increased mortality 10 years after diagnosis in a Europe-wide population based cohort. Gut 2006b;55:510-518.

Wolters FL, Joling C, Russel MG, Sijbrandij J, De Bruin M, Odes S, Riis L, Munkholm P, Bodini P, Ryan B, O'Morain C, Mouzas IA, Tsianos E, Vermeire S, Monteiro E, Limonard C, Vatn M, Fornaciari G, Rodriguez D, Groot W, Moum B, Stockbrügger RW on behalf of the European Collaborative Study Group on Inflammatory Bowel Disease (EC-IBD). Treatment inferred disease severity in Crohn's disease: evidence for a European gradient of disease course. Scand J Gastroenterol 2007;42:333-344.

Wright JP, Froggatt J, O'Keefe EA, Ackerman S, Watermeyer S, Louw J, Adams G, Girdwood AH, Burns DG, Marks IN. The epidemiology of inflammatory bowel disease in Cape Town 1980-1984. S Afr M 1986;70:10-15.

Wändell PE. Quality of life in patients with diabetes mellitus. An overview of research in primary health care in the Nordic countries. Scand J Prim Health Care 2005;23:68-74.

Yacavone RF, Locke GR, Provenzale DT, Eisen GM. Quality of life measurement in gastroenterology: what is available? Am J Gastroenterol 2001;96:285-297.

Yamamoto H, Sekine Y, Sato Y, Higashizawa T, Miyata T, Iino S, Ido K, Sugano K. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc 2001;53:216-220.

Yamamoto T, Nakahigashi M, Saniabadi AR. Review article: diet and inflammatory bowel disease – epidemiology and treatment. Aliment Pharmacol Ther 2009;30:99-112.

Yang H, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JI. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. Gut 1993;34:517-524.

Zahn A, Hinz U, Karner M, Ehehalt R, Stremmel W. Health-related quality of life correlates with clinical and endoscopic activity indexes but not with demographic features in patients with ulcerative colitis. Inflamm Bowel Dis 2006;12:1058-1067.

Öresland T, Fasth S, Nordgren S, Hultén L. The clinical and functional outcome after restorative proctocolectomy. A prospective study in 100 patients. Int J Colorect Dis 1989;4:50-56.

A

Terveyteen liittyvän elämänlaadun kyselylomake (15d©)

Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkatkaa sitten rasti (x) sen vaihtoehdon kohdalle, joka parhaiten kuvaa nykyistä terveydentilaanne. On tärkeää, että vastaatte kaikkiin 15 kysymykseen rastittamalla kustakin yhden vaihtoehdon.

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1. Liikuntakyky

1 Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa. ☐1
2 Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia. ☐2
3 Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana. ☐3
4 Pystyn kävelemään sisälläkin vain toisen avustamana. ☐4
5 Olen täysin liikuntakyvytön ja vuoteenoma. ☐5

2. Näkö

1 Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman). ☐1
2 Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman). ☐2
3 Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman). ☐3
4 En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta. ☐4
5 En näe kulkea oppaatta eli olen lähes tai täysin sokea. ☐5

3. Kuulo

1 Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman). ☐1
2 Kuulen normaalia puheääntä pienin vaikeuksin. ☐2
3 Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä. ☐3
4 Kuulen kovaakin puheääntä heikosti; olen melkein kuuro. ☐4
5 Olen täysin kuuro. ☐5

4. Hengitys

1 Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia. ☐1
2 Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä. ☐2
3 Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni. ☐3
4 Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa. ☐4
5 Minulla on hengenahdistusta lähes koko ajan, myös levossa. ☐5

5. Nukkuminen

1 Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen. ☐1
2 Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä. ☐2
3 Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä. ☐3
4 Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain. ☐4
5 Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä. ☐5

6. Syöminen

1 Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia. ☐1
2 Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin). ☐2
3 Tarvitsen hieman toisen apua syömisessä. ☐3
4 En pysty syömään itse lainkaan, vaan minua pitää syöttää. ☐4
5 En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti. ☐5

7. Puhuminen

1 Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti. ☐1
2 Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta. ☐2
3 Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen. ☐3
4 Muilla on vaikeuksia ymmärtää puhettani. ☐4
5 Pystyn ilmaisemaan itseäni vain elein. ☐5

8. Eritystoiminta

1 Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta. ☐1
2 Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa. ☐2
3 Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli. ☐3
4 Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta. ☐4
5 En hallitse lainkaan virtsaamista ja/tai ulostamista. ☐5

9. Tavanomaiset toiminnot

1 Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot). ☐1
2 Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin. ☐2
3 Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi. ☐3
4 Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin. ☐4
5 En pysty suoriutumaan lainkaan tavanomaisista toiminnoista. ☐5

10. Henkinen toiminta

1 Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti. ☐1

2 Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti. ☐2
3 Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä. ☐3
4 Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä. ☐4
5 Olen koko ajan sekaisin ja vailla ajan tai paikan tajua ☐5

11. Vaivat ja oireet

1 Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne. ☐1
2 Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoin vointia, kutinaa jne. ☐2
3 Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne. ☐3
4 Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne. ☐4
5 Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne. ☐5

12. Masentuneisuus

1 En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi. ☐1
2 Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi. ☐2
3 Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi. ☐3
4 Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi. ☐4
5 Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi. ☐5

13. Ahdistuneisuus

1 En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi. ☐1
2 Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi. ☐2
3 Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi. ☐3
4 Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi. ☐4
5 Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi. ☐5

14. Energisyys

1 Tunnen itseni terveeksi ja elinvoimaiseksi. ☐1
2 Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi. ☐2
3 Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi. ☐3
4 Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi". ☐4
5 Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi". ☐5

15. Sukupuolielämä

1 Terveydentilani ei vaikeuta miten kään sukupuolielämääni. ☐1
2 Terveydentilani vaikeuttaa hieman sukupuolielämääni. ☐2
3 Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni. ☐3
4 Terveydentilani tekee sukupuoli elämäni lähes mahdottomaksi. ☐4
5 Terveydentilani tekee sukupuolielämäni mahdottomaksi. ☐5

EFCCA Survey Questionnaire

(EFCCA = European Federation of Crohn's and Ulcerative Colitis Association)
Kyselyä on modifioitu Suomen oloihin sopivaksi.

Merkitkää rastilla vastauksenne kussakin kohdassa olevaan ruutuun.

Henkilön tietoihin ja sairaushistoriaan liittyvät kysymykset

1. Sukupuoli
a) Mies ☐ 1
b) Nainen ☐ 2

2. a) Siviilisääty
Naimaton ☐ 1
Naimisissa ☐ 2
Avoliitossa ☐ 3
Leski ☐ 4
Eronnut tai asumuserossa ☐ 5

2. b) Mikä on koulutuksenne (korkein loppuun suoritettu koulutus)
Peruskoulu tai vähemmän ☐ 1
Lukio ☐ 2
Opistotasoinen koulutus ☐ 3
Ammattikorkeakoulu ☐ 4
Yliopisto ☐ 5

2. c) Minkälaista työaikaa noudatatte
Säännöllinen päivätyö ☐ 1
2-vuorotyö ☐ 2
3-vuorotyö ☐ 3
Yötyö ☐ 4
Muu epäsäännöllinen työ ☐ 5
Osa-aikatyö ☐ 6
En ole töissä ☐ 7

2. d) Jos olette eläkkeellä, onko eläkkeenne peruste
Suolistosairaus ☐ 1
Muu sairaus ☐ 2
Muu syy, esim. ikä ☐ 3

3. Äidinkieli
a) Suomi ☐ 1
b) Ruotsi ☐ 2
c) Jokin muu, mikä _____

4. Onko Teillä diagnosoitu?
a) Crohnin tauti ☐ 1
b) Haavainen paksusuolen tulehdus eli ulseratiivinen koliitti ☐ 2
c) vain peräsuolen rajoittuva haavainen paksusuolen tulehdus (proktiitti) ☐ 3
d) Välimuotoinen (indeterminate) koliitti ☐ 4
e) Ei mikään näistä ☐ 5

5. Muu tulehduksellinen suolistosairaus
a) Mikroskooppinen koliitti (lymfosytäärinen tai kollageenikoliitti) ☐ 1
b) Jokin muu tulehduksellinen suolistosairaus, mikä _____ _____ ☐ 2
c) Ei mitään tulehduksellista suolistosairautta ☐ 3

(Jos olette vastannut kohtiin 4 – 5 Ei, Teidän ei tarvitse jatkaa tämän kyselyn täyttöä.)

6. Kuinka monta vuotta sitten edellä mainittu tauti on Teillä diagnosoitu?
_____ vuotta sitten

7. Onko lähisukulaisellanne (vanhemmat, sisarukset tai lapset) diagnosoitu Crohnin tauti tai haavainen paksusuolen tulehdus?
a) Kyllä ☐ 1
b) Ei ☐ 2

8. Minkä alan lääkäri diagnosoi Teillä Crohnin taudin tai haavaisen paksunsuolen tulehduksen?
a) Terveyskeskus- tai työterveyslääkäri ☐ 1
b) Erikoislääkäri tai sairaalalääkäri (sisätauti–lääkäri, gastroenterologi tai kirurgi) ☐ 2
c) Muu lääkäri ☐ 3

9. Minkä alan lääkäri hoitaa sairauttanne (Crohnin tauti tai haavainen paksunsuolen tulehdus)? Voitte merkata tässä useamman vaihtoehdon.

a) Terveyskeskus- tai työterveyslääkäri ☐ 1
b) Erikoislääkäri tai sairaalalääkäri (sisätautilääkäri, gastroenterologi tai kirurgi) ☐ 2
c) Muu lääkäri ☐ 3

10. Jos vastauksenne edellisessä oli "Erikoislääkäri (sisätautilääkäri, gastroenterologi tai kirurgi)", kuinka monta vuotta Teillä oli oireita ennen kuin tapasitte erikoislääkärin? _____ vuotta

11. Onko Teillä diagnosoitu jokin seuraavista sairauksista?

a) Nivelreuma ☐ 1
b) Selkärankareuma ☐ 2
c) Psoriasis ☐ 3
d) Psoriasikseen liittyvä nivelvaiva ☐ 4
e) Silmän värikalvon tulehdus tai vastaava ☐ 5

Hoito

12. Ennen nykyistä hoitoanne, oletteko saanut aiemmin jotain seuraavista hoidoista ja jos, kuinka kauan? *Merkatkaa rastilla kaikki saamanne hoidot ja ilmoittakaa hoidon kesto vuosina. Yleisimmät ns. kauppanimet em. valmisteille on lueteltu suluissa.*

a) Solunsalpaajahoito (Azamun®, Imurel®, Merkaptopurin®, Trexan®). ☐ 1
Hoidon kesto vuosina _____
b) Kortisoni (Prednison®, Prednisolon®, Medrol®, Entocort®) ☐ 2
Hoidon kesto vuosina _____
c) 5-aminosalisylaatti (5-ASA) (Asacol®,Pentasa®, Dipentum®, Salazopyrin®) ☐ 3
Hoidon kesto vuosina _____
d) Antibiootit (Trikozol®, Flagyl®, Ciprofloxacin®, Zeclar®) ☐ 4
Hoidon kesto vuosina
e) Siklosporiini (Sandimmun Neoral®) ☐ 5
Hoidon kesto vuosina _____
f) Biologiset lääkkeet (Remicade®) ☐ 6
Hoidon kesto vuosina _____
g) Leikkaushoito ☐ 7
h) Adacolumn® hoito ☐ 8
i) En tiedä mitä hoitoja olen saanut ☐ 9
j) Toistaiseksi ei ole ollut käytössä hoitoja ☐ 10
k) Paikallishoitovalmisteet (peräpuikot, peräruiskeet) ☐ 11
l) Muu lääke tai hoito suolistosairauteenne ☐ 12

_____

13. Mitä hoitoa saatte tällä hetkellä Crohnin tautiin tai haavaiseen paksunsuolen tulehdukseen? *Merkatkaa rastilla kaikki saamanne hoidot ja ilmoittakaa hoidon kesto vuosina. Yleisimmät ns. kauppanimet em. valmisteille on lueteltu suluissa.*

a) Solunsalpaajahoito (Azamun®, Imurel®, Merkaptopurin®, Trexan®). ☐ 1
Hoidon kesto vuosina _____
b) Kortisoni (Prednison®, Prednisolon®, Medrol®, Entocort®) ☐ 2
Hoidon kesto vuosina _____
c) 5-aminosalisylaatti (5-ASA) (Asacol®,Pentasa®, Dipentum®, Salazopyrin®) ☐ 3
Hoidon kesto vuosina _____
d) Antibiootit (Trikozol®, Flagyl®, Ciprofloxacin®, Zeclar®) ☐ 4
Hoidon kesto vuosina _____
e) Siklosporiini (Sandimmun Neoral®) ☐ 5
Hoidon kesto vuosina _____
f) Biologiset lääkkeet (Remicade®) ☐ 6
Hoidon kesto vuosina _____
g) Leikkaushoito ☐ 7
h) Adacolumn® hoito ☐ 8
i) En tiedä mitä hoitoja olen saanut ☐ 9
j) Toistaiseksi ei ole ollut käytössä hoitoja ☐ 10
k) Paikallishoitovalmisteet (peräpuikot, peräruiskeet) ☐ 11
l) Muu lääke tai hoito suolistosairauteenne ☐ 12

_____

14. Jos vastasitte edellisten kysymysten kohtiin 12 f) ja 13 f) kyllä, minkälainen vaikutus hoidolla oli elämänlaatuunne hoitoa seuraavien kuukausien aikana?

a) Elämänlaatu parantui selvästi ☐ 1
b) Elämänlaatu parantui jonkin verran ☐ 2
c) Elämänlaatu ei parantanut ☐ 3
d) Elämänlaatu huononi ☐ 4

15. Jos vastasitte kortisonihoitoa koskeviin kysymyksiin 12 b) ja 13 b) kyllä, minkälainen vaikutus hoidolla oli elämänlaatuunne hoitoa seuraavien kuukausien aikana?

a) Elämänlaatu parantui selvästi ☐ 1
b) Elämänlaatu parantui jonkin verran ☐ 2
c) Elämänlaatu ei parantanut ☐ 3
d) Elämänlaatu huononi ☐ 4

16. Jos vastasitte solunsalpaajahoitoa koskeviin kysymyksiin 12 a) ja 13 a) kyllä, minkälainen vaikutus hoidolla oli elämänlaatunne hoitoa seuraavien kuukausien aikana?

a) Elämänlaatu parantui selvästi ☐ 1
b) Elämänlaatu parantui jonkin verran ☐ 2
c) Elämänlaatu ei parantanut ☐ 3
d) Elämänlaatu huononi ☐ 4

17. Oletteko tyytyväinen tämän hetkiseen hoitoonne?

a) Hyvin tyytyväinen ☐ 1
b) Melko tyytyväinen ☐ 2
c) Melko tyytymätön ☐ 3
d) Hyvin tyytymätön ☐ 4

18. Onko Teille tehty leikkauksia liittyen Crohnin tautiin tai haavaiseen paksunsuolen tulehdukseen?

a) Kyllä ☐ 1
Kuinka monta_____
b) Ei *(siirtykää kysymykseen 22)* ☐ 2

19. Jos vastasitte edelliseen kysymykseen 18 kyllä, kuinka määrittelisitte leikkaushoidon vaikutuksen elämänlaatuunne leikkausta seuraavien kuukausien aikana?

a) Elämänlaatu parantui selvästi ☐ 1
b) Elämänlaatu parantui jonkin verran ☐ 2
c) Elämänlaatu ei parantanut ☐ 3
d) Elämänlaatu huononi ☐ 4

20. Jos vastasitte kysymykseen 18 kyllä, ovatko taudin oireet uusineet Teillä leikkauksen jälkeen?

a) Kyllä ☐ 1
b) Ei ☐ 2

21. Jos vastasitte kysymykseen 18 kyllä, onko Teillä ollut leikkauksen jälkeisiä vakavia komplikaatioita?

a) Kyllä ☐ 1
b) Ei ☐ 2

22. Mikäli jatkossa Teille harkitaan leikkaushoitoa Crohnin taudin tai haavaiseen paksunsuolen tulehduksen vuoksi, olisitteko halukas kokeilemaan uuden tyyppistä lääkehoitoa leikkaushoidon vaihtoehtona?

a) Kyllä ☐ 1
a) Ei ☐ 2

23. Onko lääkärinne ottanut esille Crohnin taudin tai haavaisessa paksunsuolen tulehduksen hoidossa käytettävät uudet hoidot?

a) Kyllä ☐ 1
a) Ei ☐ 2

Oireiden vaikutus elämänlaatuun

24. Mitä seuraavista oireista Teillä on esiintynyt liittyen Crohnin tautiin tai haavaiseen paksunsuolen tulehdukseen? Merkatkaa kaikki sopivat vaihtoehdot.

a) kivuliaat vatsakrampit ☐ 1
b) pysyvä tai toistuva ripuli ☐ 2
c) ruokahaluttomuus ☐ 3
d) verentulo peräsuolesta ☐ 4
e) painon putoaminen ☐ 5
f) kuume ☐ 6
g) nivelkipu ☐ 7

h) heikotus ☐ 8
i) peräaukon suulla ihokielekkeet eli skin tagit ☐ 9
j) avanne eli märkäkäytävä (fisteli) ☐ 10
k) haavauma peräaukon seudussa ☐ 11

25. Kuinka usein Teillä esiintyy häiritseviä oireita?
a) Viikottain ☐ 1
b) Kuukausittain ☐ 2
c) Muutaman kuukauden välein ☐ 3

26. Kuinka paljon oireet häiritsevät vapaa-ajan toimintaanne tai aktiviteettejanne (esim. matkustamista, ruokailua, urheilua)?
a) Merkittävästi ☐ 1
b) Jonkin verran ☐ 2
c) Eivät lainkaan ☐ 3

27. Kuinka paljon oireet vaikuttavat työntekoonne?
a) Merkittävästi ☐ 1
b) Jonkin verran ☐ 2
c) Eivät lainkaan ☐ 3

29. Otatteko oireiden vaikutuksen elämänlaatuunne esille käydessänne lääkärissä?
a) Kyllä ☐ 1
b) Ei ☐ 2

30. Kysyykö lääkärinne oireiden vaikutusta elämänlaatuunne?
a) Kyllä ☐ 1
b) Ei *(voitte siirtyä tämän sivun loppuun)* ☐ 2

31. Jos vastasitte edelliseen kysymykseen 30 kyllä, onko lääkärinne tehnyt muutoksia hoitoonne vähentääkseen oireiden vaikutusta elämänlaatuunne?
a) Kyllä ☐ 1
b) Ei ☐ 2

FinnIBDQ-tutkimukseen liityvät kysymykset
Terveyspalveluiden käyttö

1. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt vatsavaivojenne takia **terveyskeskuslääkärin** vastaanotolla?

_____ kertaa

2. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt vatsavaivojenne takia **työterveyslääkärin** vastaanotolla?

_____ kertaa

3. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt vatsavaivojenne takia **sairaalan ajanvarauspoliklinikalla** (sisätautien tai kirurgian poliklinikalla)?

_____ kertaa

4. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt vatsavaivojenne takia **sairaalan päivystyspoliklinikalla** (ensiapupoliklinikalla)?

_____ kertaa

5. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt vatsavaivojenne takia **yksityislääkärin vastaanotolla**? (Tässä ei tarkoiteta käyntejä yksityisellä lääkäriasemalla työterveyslääkärin luona)

_____ kertaa

6. Kuinka monta päivää olette ollut vatsavaivojenne vuoksi **sairaalahoidossa** viimeksi kuluneen vuoden aikana

yhteensä _____ päivää

7. Kuinka monta kertaa viimeisen vuoden aikana olette ollut vatsavaivojenne vuoksi yhteydessä **puhelimitse** sairaanhoitajan tai lääkäriin?

_____ kertaa

8. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt lääkärin vastaanotolla muiden syiden kuin vatsavaivojen vuoksi? _____ kertaa

9. Kuinka usein viimeksi kuluneen 3 kuukauden aikana vatsaoireenne ovat haitanneet Teidän työntekoanne töissä ollessanne?

- Ei ollenkaan ☐ 1
- Harvemmin kuin 2 päivänä kuukaudessa ☐ 2
- 2–3 päivänä kuukaudessa ☐ 3
- 1–2 päivänä viikossa ☐ 4
- 3 päivänä viikossa tai useammin ☐ 5
- En ole ollut töissä viimeisten 3 kuukauden aikana ☐ 6

10. Kuinka monta päivää olette ollut vatsavaivojen takia poissa töistä viimeisen vuoden aikana?

_____ (päivää)

_____ (X, jos ette ole olleet työelämässä viimeisen vuoden aikana)

11. Kuinka monta kertaa Teille on tehty vatsavaivojenne vuoksi seuraavia tutkimuksia viimeisen vuoden aikana?

- Paksusuolen tähystys? _____ kertaa
- Paksusuolen röntgenkuvaus? _____ kertaa
- Mahalaukun tähystys? _____ kertaa
- Vatsan alueen ultraäänitutkimus? _____ kertaa
- Vatsan alueen tietokonetomografiakuvaus? _____ kertaa
- Vatsan alueen magneettikuvaus? _____ kertaa

Kiitos vaivannäöstänne.